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# THE STRUCTURE OF THE CARBONYL RING OF LYCOPODINE

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By

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SCOPE AND CONTENTS:

The structure of lycopodine was investigated in the neighbourhood of the carbonyl group. The results obtained enabled the elucidation of a large part of the peripheral structure of the alkaloid.

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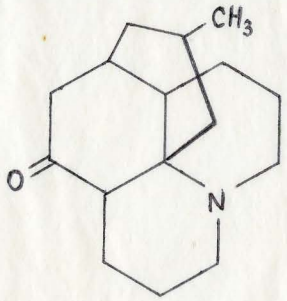
## GENERAL INTRODUCTION

Lycopodine, $C_{16}H_{25}ON$, was the first Lycopodium alkaloid to be isolated. It was obtained nearly eighty years ago by Bödeker from Lycopodium complanatum. Within the last twenty years many other alkaloids have been isolated from the Lycopodium species and now over fifty alkaloids have been isolated and characterized.

In 1958 the structure of annotinine was elucidated. Two years later the following total structure was proposed for lycopodine.




The elucidation of the structure of lycopodine automatically furnished the structures for three Lycopodium alkaloids, L-14, L-2 and dihydrolycopodine, which had been related to it. Shortly after the structure of lycopodine was announced the structures for ten other Lycopodium alkaloids were established. A list of these alkaloids is given below.

α-Obscurine, $C_{17}H_{26}ON_2$.

β-Obscurine, $C_{17}H_{24}ON_2$.

Lycodine, $C_{16}H_{22}N_2$.

Selagine, $C_{15}H_{18}ON_2$.

Acrifoline, $C_{16}H_{23}O_2N$.

Annofoline, $C_{16}H_{25}O_2N$.

Fawcettiine, $C_{18}H_{29}O_3N$.

Lofoline, $C_{18}H_{29}O_3N$.

Acetyl-fawcettiine, $C_{20}H_{31}NO_4$.

Clavolonine, $C_{16}H_{25}O_2N$.

In this investigation information was obtained pertaining to the structure of lycopodine in the neighbourhood of the carbonyl group. This information in combination with data obtained by Harrison enabled the elucidation of a large part of the peripheral structure of lycopodine.

An attempt was made to establish unambiguously the configuration of the asymmetric center adjacent to the carbonyl group but this project was not entirely successful.

## HISTORICAL INTRODUCTION

The presence of an alkaloid in a plant of the genus Lycopodiaceae was first demonstrated by Bödeker (1), who isolated a crystalline base melting at 114-115° from Lycopodium complanatum. Bödeker assigned to this Lycopodium alkaloid the formula $C_{32}H_{52}O_3N_2$ and the name lycopodine.

In 1892 Arata and Canzoneri (2) extracted and isolated from L. Saururus Lam. a base, $C_{15}H_{20}ON_2$, which they named pillijanine. No further work was done on the Lycopodium alkaloids until almost fifty years later.

In 1938 Achmatowicz and Uzieblo (3) isolated three alkaloids from L. clavatum. The most abundant melted at 115-116° and analyzed for $C_{16}H_{25}ON$. This alkaloid was undoubtedly identical with lycopodine obtained earlier by Bödeker. The other two alkaloids, which were named clavatine and clavatoxine, were assigned respectively the formulae $C_{16}H_{25}O_2N$ and $C_{17}H_{27}O_2N$.

In 1942 Deulofeu and De Langhe (4) reinvestigated L. saururus and isolated two bases which they designated saururine, $C_{10}H_{19}N$, and sauroxine, $C_{17}H_{26}ON_2$. They failed to obtain an alkaloid with the properties of pillijanine, described earlier by Arota and Canzoneri.

At this time Manske and Marion initiated a thorough investigation of the alkaloidal content of many Lycopodium species. They reported in a series of papers (5-14) the isolation of over thirty bases. From L. complanatum (re-identified later (8) as L. flabelliforme Fern.) they isolated nicotine, lycopodine and six new alkaloids. L. clavatum (10) was found to contain lycopodine, nicotine and three other alkaloids. Clavatine and clavatoxine which were reported (3)

to be present in this species of European origin were not found in the Canadian plant.

Other lycopodium alkaloids were isolated from plant material of European (15-17) and West Indian origin (18).

The list of known Lycopodium alkaloids amounts to more than fifty. Lycopodine is the major alkaloid of at least six Lycopodium species and has been found in all but three of the species which have been examined.

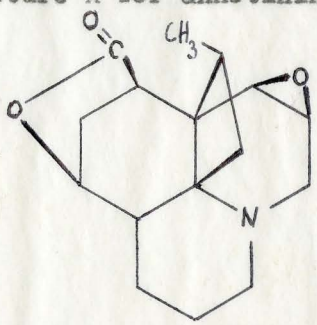
To date, structural studies have been carried out on annotinine, lycopodine, α- and β- obscurine, lycodine, Selagine, acrifoline, annofoline, fawcettiine, lofoline, and clavolonine. Annotinine was found to have a unique structure. The other Lycopodium alkaloids with a single nitrogen atom have the same skeletal structure as lycopodine. This is not surprising since the latter is the most abundant alkaloid of the Lycopodium species. The Lycopodium alkaloids having the skeletal structure of lycopodine are acrifoline, annofoline, fawcettiine, lofoline and clavolonine. Another group of Lycopodium alkaloids contain two nitrogen atoms; α-obscurine, β-obscurine, lycodine and selagine. These alkaloids are more closely related in structure to lycopodine than to annotinine.

In the following sections an account will be given of the structural investigation of these alkaloids.

Annotinine

The structure of annotine, $C_{16}H_{21}O_3N$, was the first to be elucidated. Wiesner et al (19), on the basis of chemical evidence, were able to elucidate the structure of this alkaloid and to assign configurations to most asymmetric centers. Przybylska and Marion (20) subjected annotinine to an x-ray crystallographic study and verified the results

obtained previously by Wiesner, establishing furthermore the configuration of one asymmetric center which had not been revealed on the basis of the degradative study. Finally Wiesner and co-workers (21) in 1958 gave a detailed account of the experiments that permitted the derivation of the complete structure A for annotinine.




A

Lycopodine

Two years after the elucidation of the structure of annotinine Harrison and Mac Lean (22) proposed a total structure for lycopodine. Only a summary of the degradative work done on this alkaloid, prior or during the investigation which will be described in this thesis, will be given here since a detailed account of the chemistry of lycopodine has already appeared (23).

In 1938 Achmatowicz and Uzieblo (3) assigned the correct molecula formula, $C_{16}H_{25}ON$, to lycopodine and investigated the nature of its functional groups. They found that the molecule contained no N-methyl or O-methyl groups and no active hydrogen. They also reported that the alkaloid failed to hydrogenate in the presence of palladium on charcoal or to react with carbonyl group reagents.

The failure of lycopodine to hydrogenate over Raney nickel at high pressures coupled with its inertness toward phenyl-magnesium bromide, led Marion and Manske (6) to suggest that the oxygen was

probably present in a cyclic ether linkage. These authors also reported that the dehydrogenation of lycopodine with selenium yielded a complex mixture from which it was possible to isolate five bases. Two of these were identified as 7-methyl-quinoline and 5:7-dimethyl-quinoline. 7-Methyl-quinoline was obtained from the alkaloid in two other ways; in one experiment lycopodine was heated with palladium-barium-sulphate and in the other with phthalic anhydride. It was pointed out that the formation of 7-methyl-quinoline by dehydrogenation of lycopodine with three different reagents strongly suggested that no rearrangements were involved in the process. It was thus concluded that the quinoline nucleus, completely hydrogenated, was present as such in the molecule.

In 1950 Mac Lean, Manske and Marion (24) showed that the oxygen atom in lycopodine I was present in a carbonyl group and not in an ether linkage as believed previously. They found that the infrared spectrum of the alkaloid had an absorption band at 1693 $cm^{-1}$ which was in the region of carbonyl absorption. The presence of a carbonyl group was confirmed by preparation of a hydrazone, by hydride reduction of lycopodine to dihydrolycopodine II and by formation of a tertiary alcohol on treatment of I with phenyl lithium.

Mac Lean, Manske and Marion attempted without success to degrade lycopodine through its N-oxide as well as by the Emde and Hofmann reactions. However, degredation of lycopodine by the method of von Braun was successful and resulted in the formation of two isomeric bromides, $C_{17}H_{25}ON_2Br$, which were designated α- and β- cyanobromolycopodine III and IV. α-Cyanobromolycopodine III was converted by the action of potassium acetate in ethanol to α-cyanoacetoxylycopodine V. On alkaline

hydrolysis V gave an alcohol, α-cyanohydroxylycopodine VI. Chromic acid oxidation of compound VI produced an amorphous acid VII, yielding a crystalline methyl ester VIII which analyzed for $C_{18}H_{26}O_3N_2$. The oxidation of VI to VII without loss of carbon showed that VI was a primary alcohol. It was thus proved that the ring cleaved on formation of α-cyanobromolycopodine III contained a methylene group next to the nitrogen atom.

α-Cyanobromolycopodine III on being heated with methanolic potassium hydroxide gave rise to a compound IX, $C_{17}H_{24}ON_2$, which was found to be resistant to oxidation with potassium permanganate, chromic acid or ozone. It also failed to take up hydrogen on catalytic hydrogenation. It was assumed that the formation of IX involved a cyclization reaction with loss of hydrogen bromide. Since the reaction of III with potassium hydroxide failed to introduce a terminal double bond another route was followed that might lead to the desired objective. α-Cyanobromolycopodine III was treated with trimethylamine to give a quaternary bromide X which was converted to the corresponding quaternary base. Pyrolysis in vacuo of the latter yielded two products, one was cyclized compound IX while the other was a base XI formed from the quaternary hydroxide by the loss of methanol.

When bromocyanamide III was hydrogenated over a palladium-calcium carbonate catalyst, α-cyanolycopodine XII was obtained by replacement of the bromine by hydrogen.

β-Cyanobromolycopodine IV, the minor product from the von Braun reaction, gave, by the action of boiling ethanolic potassium acetate, a product XIII isomeric with IX. Compound XIII was resistant to oxidation or catalytic hydrogenation and it was concluded that it, too, was formed

in a

in a cyclization reaction. The compounds described by Mac Lean, Manske and Marion proved to be key compounds in the subsequent structural investigations. The reactions studied by Mac Lean, Manske and Marion are summarized in fig. 1.

Douglas, Lewis and Marion (25) were able to relate lycopodine to the minor Lycopodium alkaloids L14 and L2. The first XIV, $C_{16}H_{25}N$ was obtained by dehydration of dihydrolycopodine II with phosphorous pentachloride, while the second was shown to be acetyl-dihydrolycopodine XV, $C_{18}H_{29}O_2N$.

In 1956 Barclay and Mac Lean (26) resumed the structural study of lycopodine. They reported the reaction of α-cyanolycopodine XII with bromine. The bromination of XII in carbon tetrachloride solution yielded an amorphous solid precipitate from which a crystalline monobromo derivative XVI was obtained in low yield. Compound XVI in contact with aqueous alkali readily lost its bromine to give a mixture of uncharacterized compounds. Treatment of the amorphous precipitate, remaining after the separation of XVI, with aqueous alkali gave a crystalline alkali-soluble product XVII, $C_{17}H_{24}O_2N_2$, whose infrared and ultraviolet spectra were consistent with an α-diketone in the enol form. It was concluded that the bromination product contained an α,α-dibromo derivative of ketone XII, a fact indicating the presence of a methylene group next to the carbonyl in both α-cyanolycopodine XII and therefore in lycopodine itself.

Additional evidence for the presence of a methylene group, adjacent to the carbonyl, in α-cyanolycopodine XII and lycopodine I came from the fact that the former, on being treated with benzaldehyde in the presence of sodium methoxide, gave a benzylidene derivative XVIII, $C_{24}H_{30}ON_2$.

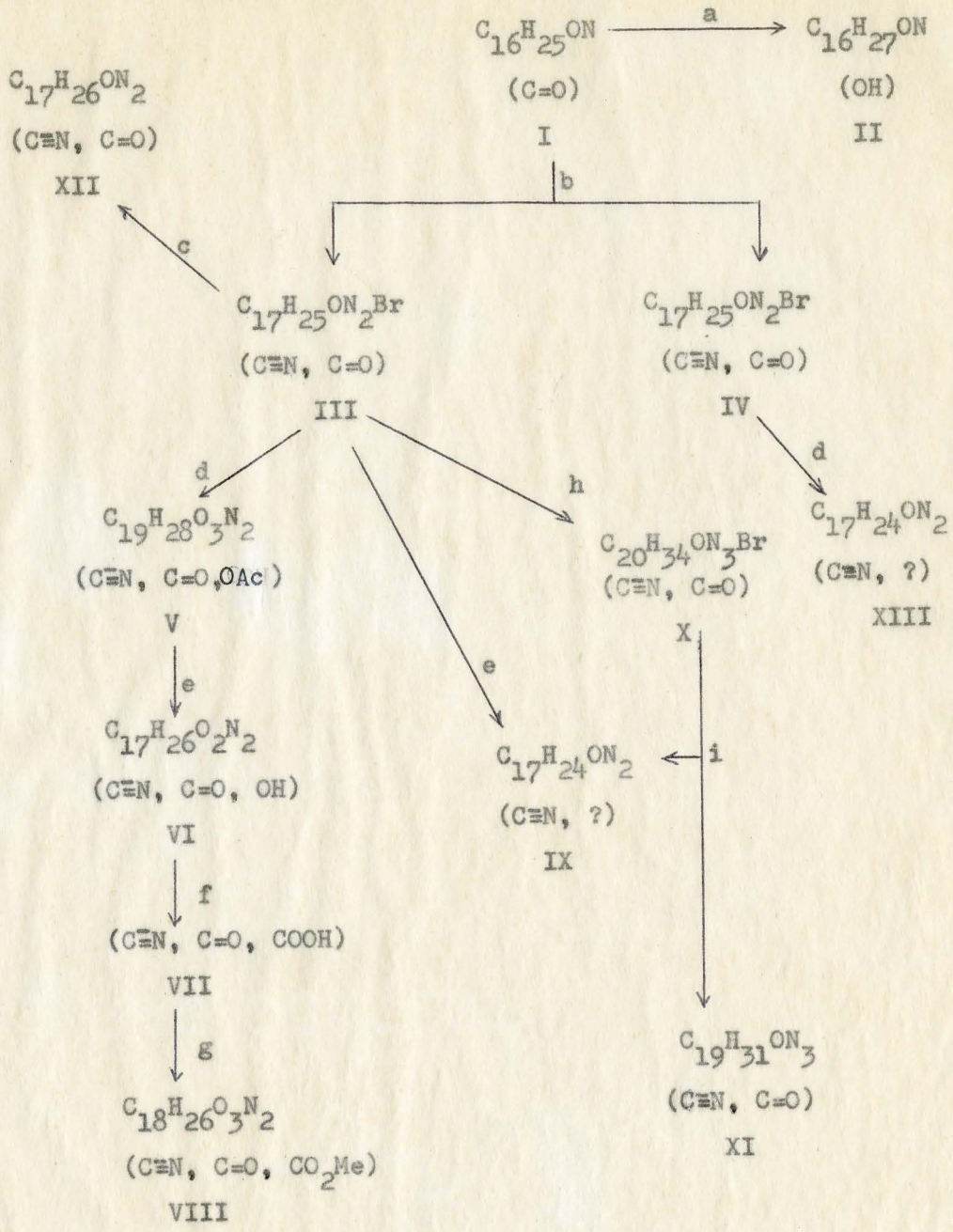



Fig. 1

a. $LiAlH_4$

b. BrCN

c. $H_2$, Pd-$CaCO_3$

d. KOAc in boiling EtOH

e. KOH in boiling MeOH

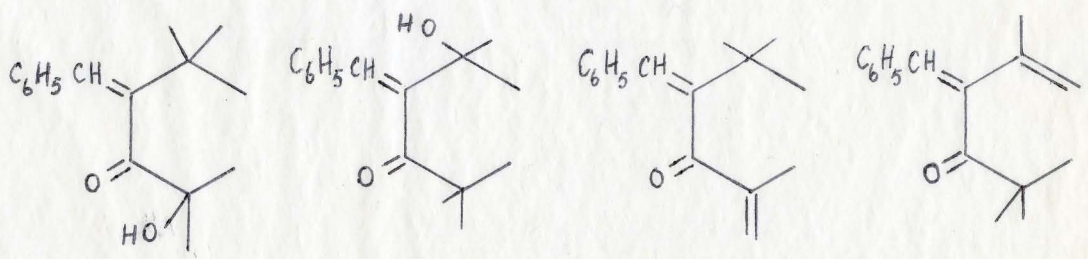
f. $CrO_3$ in AcOH

g. $CH_2N_2$

h. $Me_3N$

i. 1. $Ag_2O$
2. pyrolysis

Later Barclay (27) investigated the oxidation of the benzylidene derivative XVIII with several reagents. From the ozonolysis of XVIII, in methanolic solution, he obtained an enolic product XIX apparently different from the enol obtained previously from the bromination of compound XII. The preparation of the two enols XVII and XIX indicated that the carbonyl group in lycopodine was flanked on both sides by methylene groups. When the benzylidene derivative XVIII was ozonized in ethyl acetate solution, instead of an enol, a cyclic anhydride XX, $C_{17}H_{24}O_3N_2$, was formed. Treatment of the benzylidene compound XVIII with selenium dioxide gave two products: one of these was a hydroxy compound XXI, $C_{24}H_{30}O_2N_2$, while the other was a yellow olefinic compound XXII, $C_{24}H_{28}ON_2$. The infrared spectrum of XXI suggested that the hydroxyl group was axial and alpha to the carbonyl group. The ultraviolet spectrum of the unsaturated compound XXII was consistent with that of an $\alpha,\beta$ unsaturated ketone. The partial structures $XXI_a$ and $XXII_a$ were proposed for these two compounds but the evidence at hand did not rule out $XXI_b$ and $XXII_b$.



$XXI_a$ $XXI_b$ $XXII_a$ $XXII_b$

The reactions described above which were carried out by Barclay are summarized in fig. 2.

Barclay also carried out some dehydrogenation experiments. XII

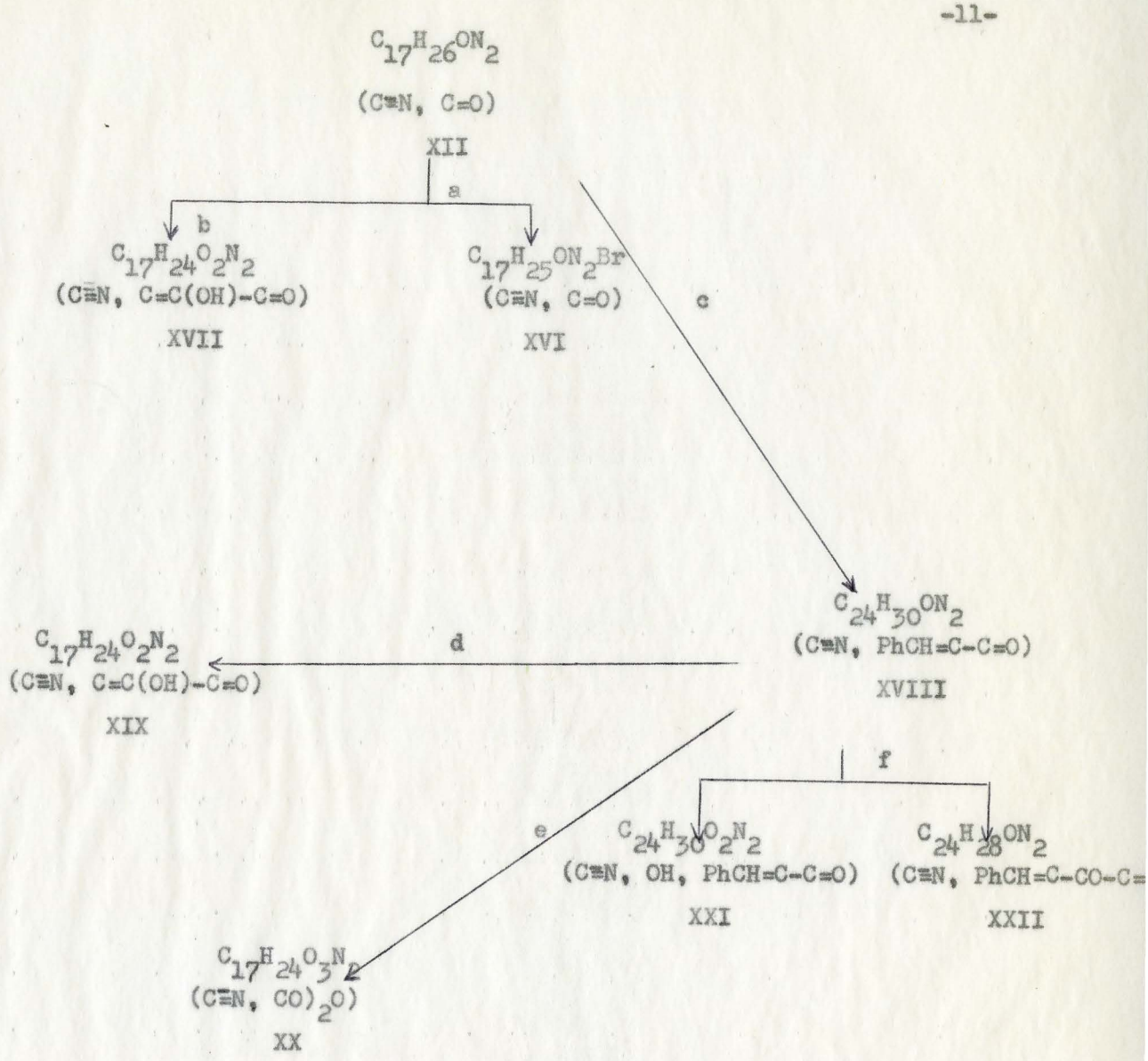



Fig. 2

a. Br in $CCl_4$

b. 5% KOH in aq. dioxane

c. $C_6H_5CHO$, NaOMe

d. $O_3$ in MeOH

e. $O_3$ in EtOAc

f. $SeO_2$

The base XXIII, $C_{16}H_{29}ON$, derived from α-cyanolycopodine XII by hydrolysis of the nitrile group and reduction of the carbonyl function was used in one of these experiments. Dehydrogenation of XXIII with palladium-charcoal yielded a small amount of a product which, from spectroscopic evidence, appeared to be an alkylated quinoline. It was proposed, therefore, that a reduced quinoline ring system was present in lycopodine derivatives of the "α-series".

Harrison (28) was able to gain information pertaining to the size of the ring cleaved on formation of the α-bromocyanamide III. This ring will be designated hereafter as "ring A" while the other nitrogen ring, cleaved on formation of β-cyanobromolycopodine IV will be labelled B. Acid VII was hydrolyzed with aqueous alcoholic hydrochloric acid to yield the corresponding amino acid hydrochloride XXIV. Treatment of XXIV with diazomethane yielded a mixture of an amino ester and a lactam XXV, $C_{16}H_{23}O_2N$. The latter had an infrared absorption band at 1635 $cm^{-1}$ which is characteristic of six-membered or larger ring lactams. Reduction of the lactam XXV with lithium aluminum hydride yielded dihydrolycopodine. It was, therefore, concluded that no skeletal rearrangement had occurred in the above reaction sequence and, consequently, that ring A was six-membered or larger.

Harrison was able to prepare β-cyanohydroxylycopodine XXVI by reacting the β-cyanobromide IV with silver acetate in benzene and then hydrolyzing the acetate formed. Chromic acid oxidation of compound XXVI gave (23) a non-crystalline keto-acid XXVII which was converted to a crystalline methyl ester XXVIII, $C_{18}H_{26}O_3N_2$, on treatment with diazomethane. As no loss in carbon had occurred in the oxidation reaction it was con-

cluded that XXVI was a primary alcohol. The acid XXVII was converted to a lactam XXIX, $C_{16}H_{23}O_2N$, by a series of reactions analogous to those used to obtain lactam XXV. On lithium aluminum hydride reduction compound XXIX was converted to dihydrolycopodine II. It was, therefore, concluded that the lactam ring is of the size of ring B. The infrared spectrum of XXIX was consistent with that of a six- or larger-membered lactam. Hence it followed that ring B in lycopodine is six-membered or larger. Harrison was able to obtain further information by a study of the keto-acid XXVII. Reduction of this acid with sodium borohydride yielded a neutral product XXX, $C_{17}H_{24}O_2N_2$, having an infrared spectrum (peak at 1743 $cm^{-1}$ in nujol and at 1761 $cm^{-1}$ in carbon tetrachloride solution) that indicated the presence of a five- or six-membered lactone ring. Hence it was concluded that the carbonyl group was separated from the nitrogen atom by three or four carbon atoms around the periphery of ring B. The results obtained by Harrison are summarized in fig. 3.

The structural investigation described to this point made very attractive the hypothesis of the presence of the hexahydrojulolidine ring system in lycopodine. The ketonic group in lycopodine seems, on the basis of its absorption in the infrared near 1700 $cm^{-1}$, to be present in a six- or larger membered ring. This fact together with the dehydrogenation experiments of Barclay, Harrison's study on the size of rings A and B, and the existence of a hexahydrojulolidine ring system in annotinine, the only lycopodium alkaloid of known structure at the time, were all consistent and supported such a formulation. In making use of the hexahydrojulolidine ring system it was thought convenient to place the carbonyl group in the position shown

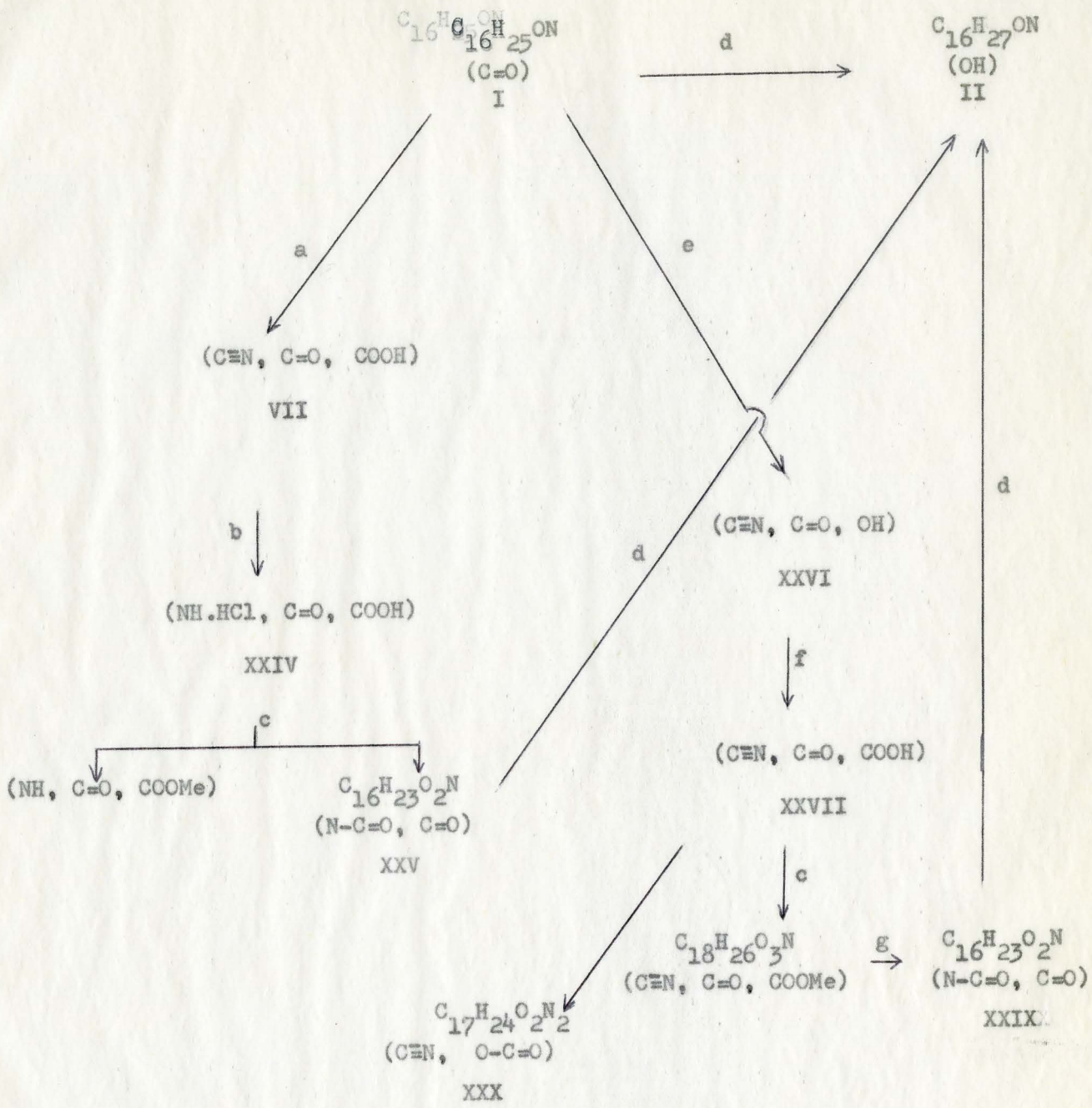



Fig. 3

a. 1. CNBr
   2. KOAc in boiling EtOH
   3. KOH in boiling MeOH
   4. $CrO_3$ in AcOH

b. 2M HCl under reflux

c. $CH_2N_2$

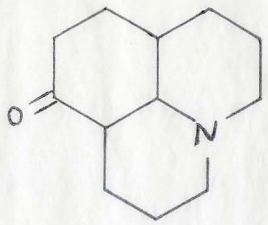
d. $LiAlH_4$

e. 1. CNBr
   2. AgOAc in boiling $C_6H_6$
   3. KOH in boiling MeOH

f. $CrO_3$ in AcOH

g. 1. 2M HCl under reflux
   2. $CH_2N_2$
   3. xylene under reflux

in the partial formula below.




B

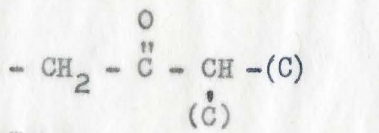
Partial structure B is compatible with the conclusions deduced regarding the relative positions of the nitrogen and carbonyl groups and also places the carbonyl group in a position corresponding to that of the lactonized hydroxyl function of annotinine. The isolation by Barclay of the two enols XVII and XIX was at variance with the hexahydrojulolidine formulation B. Harrison, however, (23) was able to show that the two compounds were in fact two different crystalline forms of the same molecular species. Carson (29) presented conclusive evidence that the carbonyl group in lycopodine is flanked on one side by a methylene group and on the other by a methine group. He found that lycopodine, when treated with sodium methoxide in deuteromethanol, exchanged three hydrogen atoms for deuterium, a fact which means that three enolizable hydrogens exist in the molecule. Three hydrogen atoms must, therefore, be present adjacent to the carbonyl group.

It has been noted previously that when β-cyanobromolycopodine IV was treated with ethanolic potassium acetate, instead of acetylation, cyclization occurred giving rise to the 'β-cyclized' compound XIII. The latter was found to form in a variety of basic media. It was obtained, for instance, when the β-cyanobromide IV was treated at room temperature with sodium borohydride. However, Harrison (23) found that when an ethanol solution of sodium borohydride was added slowly to an ice-

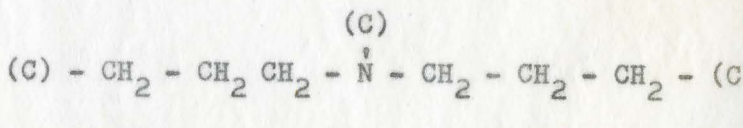
cooled ethanol solution of IV, instead of XIII, the hydroxy bromide XXXI, $C_{17}H_{27}ON_2Br$ was obtained. This compound on catalytic hydrogenation yielded β-cyanodihydrolycopodine XXXII.

α-Cyanodihydrolycopodine XXXIII (obtained from α-cyanolycopodine XII by hydride reduction) and XXXII were subjected to Kuhn-Roth oxidation. Both compounds yielded a mixture of acetic, propionic and butyric acid, while from lycopodine itself only acetic acid was obtained. The acids were separated and identified by gas chromatography of their methyl esters. These results indicated that α- and β-cyanodihydrolycopodine XXXIII and XXXII both contain a n-propyl group.

The structural investigations, carried out thus far, established rigorously the presence of the fragments C and D in the alkaloid molecule.

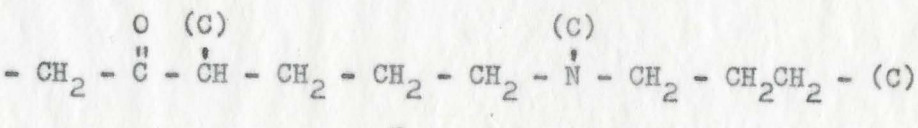


C



D

On accepting the hexahydrojulolidine formulation B it was possible to link with certainty these fragments to partial structure E.



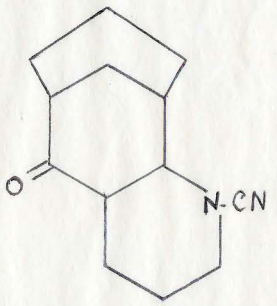
E

The presence, however, of the hexahydrojulolidine ring system in lycopodine was by no means established and another way to connect fragments C and D was yet conceivable. It was possible to write a structure in which the third methylene group in the direction of the

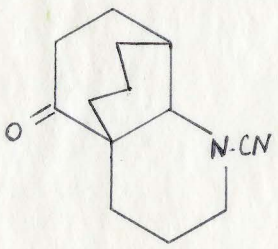
'β cleavage' was identical with the methylene adjacent to the carbonyl group in fragment C. By the work described in this thesis it was possible to assigne unambiguously partial structure E to lycopodine's molecule.

In the following paragraphs the structures of the "cyclized compounds" IX and XIII will be considered.

Song (30) was able to prove that cyclization in the formation of IX, had occurred at a position alpha to the carbonyl group. The following two partial structures were proposed by him for the 'α-cyclized' compound IX.



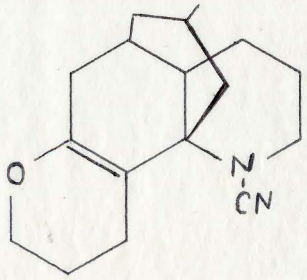

$IX_a$




$IX_b$

Carson (29) was able to differentiate between these two possibilities. He showed that α-cyclocyanolycopodine IX contained a methylene group adjacent to the carbonyl function, a fact consistent only with structure $IX_b$.

The isomeric β-cyclized compound XIII was studied by Harrison (28, 23) who presented convincing evidence that it had the structure shown below.



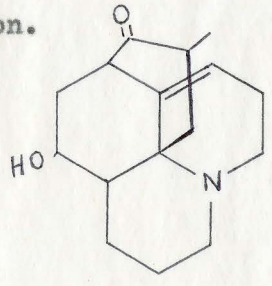

XIII

It is interesting to note that replacement of the oxygen atom in XIII with nitrogen gives rise to the ring system found in the Lycopodium alkaloids containing two nitrogens.

Acrifoline

Acrifoline, $C_{16}H_{23}O_2N$, was first isolated in 1947 by Manske and Marion (13) from L. annotinum var. acrifolium. Perry and Mac Lean (31) established that the base contains a carbonyl group, a double bond and a hydroxyl group.

Acrifoline has been subjected to an extensive structural investigation by Mac Lean and French (32). Part of this work appeared in a brief communication (33) wherein a total structure was proposed for the alkaloid. The data of Mac Lean and French that led to structure F will be discussed in this section.




F

Kuhn-Roth analysis of acrifoline indicated the presence of one C-methyl group, while N. M. R. spectroscopy showed the presence of a keto group, one olefinic proton and a secondary hydroxyl group. The infrared spectrum of crystalline acrifoline did not show carbonyl absorption which, however, appeared when the substance was dissolved in chloroform. This fact was interpreted as indicating the presence of a hemiketal in the solid state, the formation of which requires the carbonyl group to be separated from the hydroxyl carbon atom by two or three atoms.

Acrifoline methiodide underwent a Hofmann elimination, when

treated with potassium tertiary butoxide, yielding a compound with the spectral properties of a conjugated diene. Formaldehyde was formed on ozonolysis of the diene which must therefore contain a terminal methylene group. Reduction of the diene with sodium borohydride gave a diol which, on treatment with sodium in alcohol, reduced to a compound containing one olefinic double bond. A modified Kuhn-Roth oxidation of the last compound yielded acetic and propionic acids whereas acrifoline yielded only acetic acid. It follows that in the reduction of the diol the hydrogen added to the terminal double bond. Catalytic hydrogenation of the diene yielded a mixture of 1, 2 and fully reduced products. Oxidation of this mixture yielded butyric acid as well as propionic and acetic acids. Thus the presence of the system $>C=CHCH_2CH_2-N<$ in acrifoline was proved.

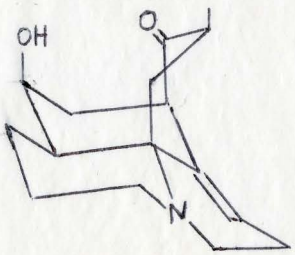
Acrifoline underwent, with cyanogen bromide, the von Braun reaction. One of the two products formed, isolated as its quaternary trimethylamonium bromide, underwent a Hofmann elimination giving rise to a neutral conjugated diene. The second product from the cyanogen bromide reaction was converted to a non-crystalline quaternary ammonium bromide. The latter, on treatment with potassium tertiary butoxide, yielded an oily neutral compound containing two isolated double bonds; one of these was proved to be terminal by the formation of formaldehyde on ozonolysis. The latter compound on catalytic reduction gave the corresponding tetrahydro compound which on Kuhn-Roth oxidation yielded butyric acid as well as propionic and acetic acids. It was thus established that acrifoline contained the grouping:

$$-\overset{|}{N}-CH_2-CH_2-CH_2-\overset{|}{C}-$$

Selenium dioxide oxidation of acrifoline gave a conjugated

carbonyl compound which on catalytic reduction was converted to dihydroacrifoline. The unsaturated compound must, therefore, contain intact the carbon skeleton of acrifoline. The study of its N. M. R. spectrum revealed the presence of a $-\overset{\overset{O}{\|}}{C}-C.CH_3=CH-$ group which must have been derived from the grouping $-\overset{\overset{O}{\|}}{C}-CH.CH_3-CH_2-$, present in acrifoline. In the selenium dioxide oxidation product a base catalyzed addition occurs of the hydroxyl group to the conjugated double bond, a fact which implies that the carbon atom β to the carbonyl group and the hydroxyl carbon are separated by two or three atoms.

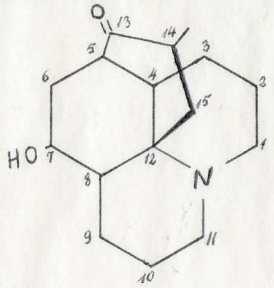
Oppenauer oxidation of dihydroacrifolinol yielded a diketone. The infrared spectrum of the diketone had strong absorption at 1700 $cm^{-1}$ indicating that both carbonyl groups are present in rings that are six membered or larger. A peak at 1420 $cm^{-1}$, not appearing in acrifoline, indicates that the diketone contains a methylene group adjacent to the carbonyl group derived from the secondary hydroxyl function of acrifoline. The formation of a hemiketal in solid acrifoline furnishes information regarding the relative stereochemistry of this alkaloid. The hydroxyl group must be axial and on the same side of the molecule as the bridge bearing the carbonyl group. Furthermore it is required that the carbonyl ring exists predominantly in the boat form as shown in the structure below.




Annofoline

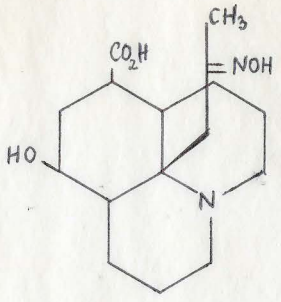
Annofoline, $C_{16}H_{25}O_2N$ was isolated from L. annotinum and was found

(34) to contain a hydroxyl group, a carbonyl group and at least one C-methyl group. Anet and Khan (35) presented evidence to show that annofoline has, most probably, structure G.




G

The infrared spectrum of annofoline in carbon tetrachloride solution was found to have a carbonyl band of abnormally low intensity, a fact suggesting the presence of a hemiketal system. The N. M. R. spectrum of the alkaloid showed that the methyl group is present as $\rangle CH\text{-}CH_3$. Oxidation of annofoline with selenium dioxide gave a dehydro-derivative which was an $\alpha\beta$-unsaturated ketone. The N. M. R. spectrum of this compound indicated the presence of the grouping $-CO\text{-}C\cdot CH_3{=}CH-$. The olefinic proton band was unsplit and therefore it appeared that the carbon next to the =CH- was quaternary. Annofoline underwent the Wolff-Kishner reduction to give dihydrodeoxy-annofoline. This compound on chromic acid oxidation gave a ketone, deoxyannofoline. The oxidation of deoxyannofoline with selenium dioxide gave a non crystalline base of weakly acidic properties which had the characteristics of an enolic $\alpha$-diketone. It was concluded that in annofoline a methylene group was present next to the hydroxyl. When annofoline was treated with t-butyl nitrite in t-butyl alcohol, in the presence of potassium hydroxide, an amphoteric compound was obtained. Evidence was presented that it had structure H.



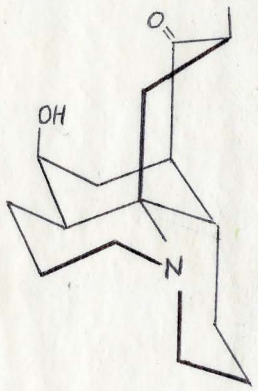

H

The latter compound on dehydrogenation in the presence of palladium-charcoal yielded julolidine, and thus strong evidence was obtained of the presence of the hexahydrojulolidine ring system in the annofoline molecule. Finally it was pointed out that the proposed structure is compatible with Conroy's biogenetic scheme (36).

In a subsequent publication (37) Anet reports the conversion of acrifoline to annofoline. He also establishes the relative stereochemistry of annofoline. It was found that acrifoline hydrobromide on catalytic hydrogenation gave not only the known dihydroacrifoline (33) but also annofoline in 10% yield. Evidently the two reduction products are epimers at C-4. Reduction of annofoline with sodium borohydride was reported (35) to yield a mixture of two products, which were designated α- and β- dihydroannofolines. β-Dihydroannofoline was found to be identical with deacetylfawcettiine (18, 35) (cf. next section). The dihydroannofolines were shown to be epimeric at C-14. Reduction with sodium borohydride under neutral conditions, or with lithium aluminum hydride in ether, gave only the α-isomer while sodium borohydride reduction in the presence of sodium hydroxide gave as much as 50% of the β-isomer. This observation indicates that the β-isomer is not a reduction product of annofoline but of a ketone having the methyl group in the opposite configuration to that of annofoline. This was confirmed by the non-identity of O-acetyl-annofoline hydrobromide and of dehydrofawcettiine

hydrobromide. However, it was found that dehydrofawcettiine hydrobromide was hydrolyzed to annofoline by base. It was, therefore concluded that annofoline is the more stable of the two isomeric ketones. Since annofoline exists (at least to some extent) in the hemiketal form, ring D must have predominantly the boat conformation and the methyl group must be equatorial to account for the stability of this alkaloid.

I depicts the stereochemistry of annofoline.



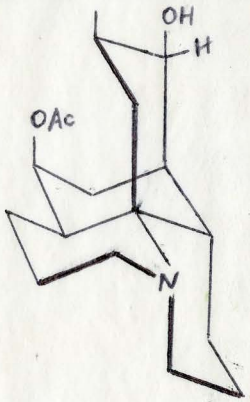

I

Fawcettiine

Fawcettiine, $C_{18}H_{29}O_3N_1$ was originally obtained from L. fawcettii. It was found (18) to contain hydroxyl and an O-acetyl groups. Hydrolysis of fawcettiine afforded the diol, deacetylfawcettiine, which undergoes ready dehydration to anhydrodeacetylfawcettiine, $C_{16}H_{25}ON$. Oxidation of fawcettiine with chromium trioxide (38) gave a ketone which on hydrolysis (deacetylation) yielded annofoline. It was thus concluded that annofoline is deacetyldehydrofawcettiine. However, Anet showed (37) (cf. previous section) that the ketone obtained on oxidation of fawcettiine is not identical with O-acetyl annofoline. The two compounds are epimeric at C-14. Anet (37) points out that the boat form of ring D in fawcettiine

is unfavorable as it places the methyl group in the crowded flag-pole position. Additional evidence indicating that ring D exists in the chair form comes from the fact that neither fawcettiine nor lofoline, which are epimeric at C-13, are hydrogen bonded in dilute carbon tetrachloride solutions.

In accordance with the above discussion J represents the structure of fawcettiine.

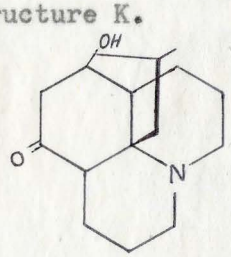



J

Another alkaloid, $C_{20}H_{31}NO_4$, obtained from L. fawcettii was shown to be (38) acetylfawcettiine; it was obtained by acetylation of fawcettiine while on hydrolysis it yielded deacetylfawcettiine.

Clavolonine

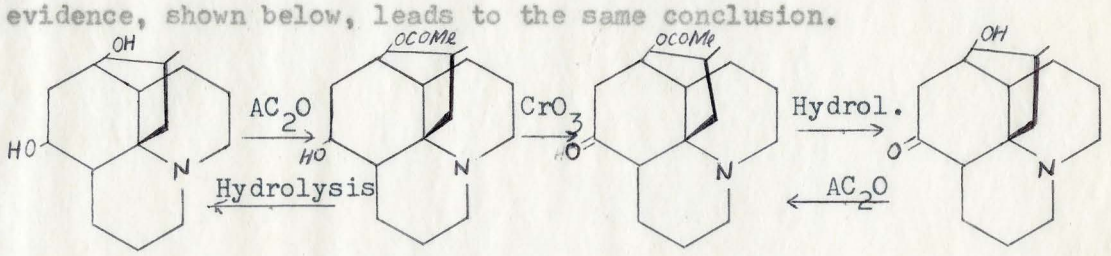
Clavolonine obtained from L. Clavatum Linn. was assigned by Burnell and Taylor (38) structure K.




K

Infrared spectroscopy indicated the presence in its molecule of a carbonyl and a hydroxyl group. Chromium trioxide oxidation of clavolonine gave a diketone, also obtained on oxidation of deacetylfawcettiine. It

was thus established that the two oxygen functional groups are located at C-7 and C-13. The presence, in the infrared spectrum of the alkaloid of a band at 1412 $cm^{-1}$ indicated that the carbonyl is flanked by a methylene group. It was, therefore, concluded that the carbonyl group occupies position C-7 while the hydroxyl is attached to C-13. Chemical evidence, shown below, leads to the same conclusion.




Deacetylfawcettiine

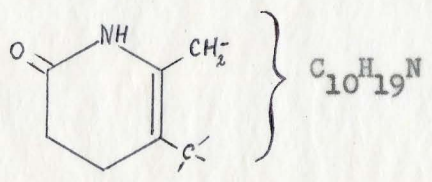
Clavolonine

α- and β-Obscurine

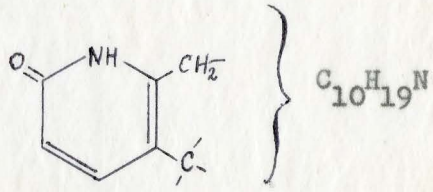
Obscurine, a minor alkaloid occuring in several Lycopodium species, was first isolated by Manske and Marion (5). Later (39) it was shown that obscurine is actually a mixture of two bases, α-obscurine, $C_{17}H_{26}ON_2$, and β-obscurine, $C_{17}H_{24}ON_2$. Dehydrogenation of α-obscurine by heating with palladium-charcoal gave rise to 7-methyl-quinoline and 6-methyl-α-pyridone. The infrared and ultraviolet spectra of β-obscurine were found to be consistent with the presence of an α-pyridone ring in the molecule. It was also found that the obscurines have only one basic nitrogen. Later it was shown (40) that both alkaloids have an N-methyl group and (40, 41) that the basic nitrogen is tertiary. The fact that both compounds show an NH stretching band in the infrared indicates that the non basic nitrogen is secondary.

Ayer and Iverach (40) were able to propose total structures for the obscurines on the basis mainly of their infrared, ultraviolet and nuclear magnetic resonance (N. M. R.) spectra and also the dehydrogenation

data of Moore and Marion (39). An account of this work will be given here. α-Obscurine does not exhibit the spectral properties of an α-pyridone but shows bands in the infrared indicating the presence of an amide group and a double bond. The dehydrogenation of α-obscurine, yielding 6-methyl α-pyridone, coupled with the above spectral data suggests the presence of a partially reduced α-pyridone ring in the alkaloid. The ultraviolet spectrum of α-obscurine (λmax 241, log ε 3.17) does not agree well with that of 6-methyl 5,6 dihydro α-pyridone and the high infrared frequencey (1700 $cm^{-1}$) of the double bond stretching vibration suggests that it is not conjugated to the carbonyl group but is attached directly to the amide nitrogen. The absence of a 5,6-dihydro-α-pyridone ring, in α-obscurine, is indicated also by N. M. R. which shows no vinylic hydrogens. The presence of a 6-methyl 3,4-dihydro-α-pyridone ring in the molecule is ruled out for the alkaloid, as shown by N. M. R., contains only one C-methyl group (Kuhn-Roth determination) present in the grouping $\rangle CH-CH_3$. The methyl group, then, in the dehydrogenation product (6-methyl α-pyridone) must have arisen from a methylene group. The selective removal of two hydrogens from α-obscurine to yield β-obscurine, unambiguously proved that α-obscurine is simply dihydro-β-obscurine. On the basis of the data cited to this point one can write the following partial structures L and M for α- and β-obscurine respectively.




$C_{10}H_{19}N$

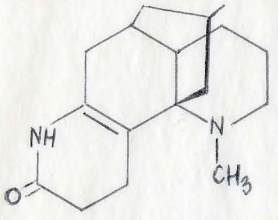



$C_{10}H_{19}N$

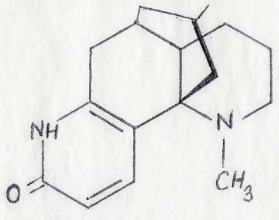
L M

It is obvious from the interconversion experiment, that the $C_{10}H_{19}N$ portion is identical in both alkaloids. Finally total structures N and

O were proposed for α- and β-obscurine. These structures provide an explanation for the formation of 7-methyl-quinoline on dehydrogenation




N

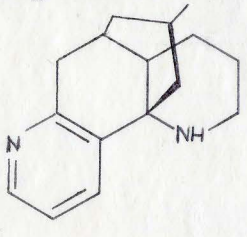



O

of α-obscurine and are, in addition, consistent with a scheme proposed by Conroy (36) for the biogenesis of Lycopodium alkaloids.

Lycodine

Lycodine was isolated in 1958 by Anet and Eves (41). These workers assigned the formula $C_{17}H_{24}N_2$ to the alkaloid and found that it contains a 2,3 disubstituted pyridine ring, a secondary nitrogen atom and a C-methyl group. Later Ayer and Iverach (40) pointed out that the analytical figures that led Anet and Eves to propose the molecular formula $C_{17}H_{24}N_2$, for lycodine, did not exclude the formula $C_{16}H_{22}N_2$. Furthermore they suggested a close relationship between this alkaloid and the obscurines, proposing for it total structure P.

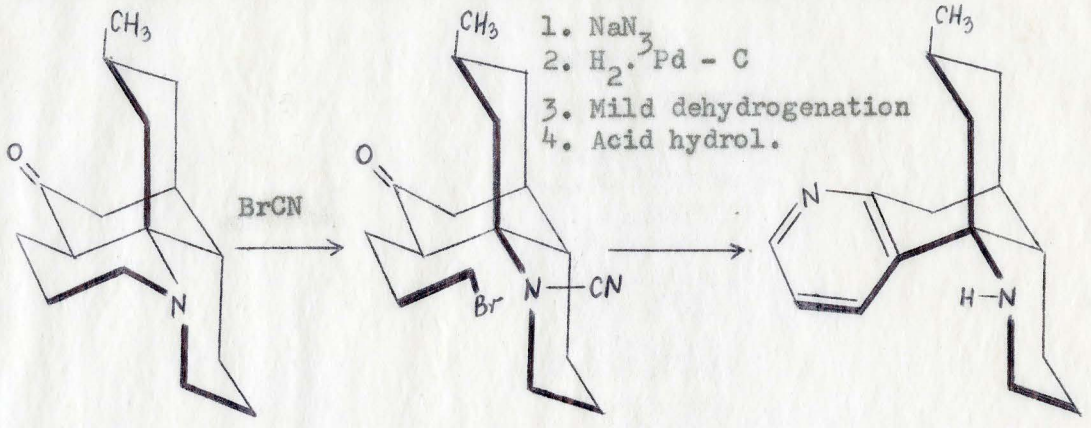



P

In a subsequent paper (42) Ayer and Iverach reported the transformation of β-obscurine to N-methyl lycodine and lycodine, thus establishing unambiguously that lycodine is the pyridine analogue of des-N-methyl-β-obscurin

By interconverting lycopodine I (by this time the structure of lycopodine was known almost with certainty) to lycodine, P, Anet and Rao

(43) confirmed the structure suggested for the latter alkaloid by Ayer and Iverach. The reactions involved are formulated below.



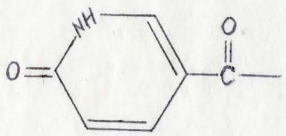

I IV Lycodine

Selagine

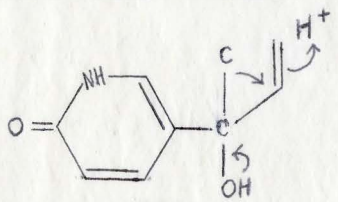
Wiesner et al (44) proposed a structure for selagine, an alkaloid isolated from L. selago. Selagine, $C_{15}H_{18}ON_2$, was found to contain a basic nitrogen atom, two C-methyl groups and an α-pyridone grouping. The N. M. R. spectrum of the alkaloid showed the presence of two protons on the pyridone ring, which must therefore be disubstituted. Reduction of selagine with Adams catalyst in acetic acid gave tetrahydroselagine, while a similar reduction in ethanol yielded dihydroselagine. The ultraviolet spectra of selagine and the reduction products were found to be identical. This fact showed that selagine contains two isolated double bonds and must therefore be tricyclic. The N. M. R. spectrum of selagine has a multiple peak at 1039 cycles/sec. (the chemical shifts were measured from the aromatic protons of toluene which were arbitrary set at 1000 cycles/sec.) corresponding to two olefinic protons, while that of dihydroselagine shows a singlet at 1045 cycles/sec. corresponding to one proton. Thus it was concluded that both isolated double bonds in

selagine are trisubstituted. The fact that the peak corresponding to the olefinic proton of dihydroselagine is unsplit indicates that there is no hydrogen in a position alpha to this proton. A study of the N. M. R. spectra of selagine, dihydroselagine and tetrahydroselagine gave important information regarding the relative position of the isolated double bonds and the two methyl groups. In selagine the highly shielded protons give rise to a peak situated at 1192 cycles/sec. In dihydroselagine a new peak appears at 1215 cycles/sec. with an integrated surface corresponding to three protons. The increased shielding of three equivalent protons in dihydroselagine was interpreted to be due to the saturation in this compound of a double bond, present in selagine, to which one of the two methyl groups is directly attached. The N. M. R. spectrum of tetrahydroselagine shows two peaks at 1216 and 1227 cycles/sec., each with an area of three protons. The second isolated double bond of selagine is, therefore, also directly attached to a methyl group. Additional information about the environment of the double bonds was obtained by oxidation of selagine, dihydroselagine and tetrahydroselagine under Kuhn-Roth conditions. On oxidation of selagine the only volatile acid formed was acetic acid, while both dihydro- and tetrahydroselagine yielded propionic acid and acetic acid. From the oxidation experiments it followed that both reduction products of selagine contain an ethyl group, while selagine itself contains an ethylidene grouping and an endocyclic double bond. Treatment of selagine with nitrous acid gave an alcohol, selaginol. The ultraviolet, infrared and N. M. R. spectra of selaginol compared very closely with those of selagine. This indicated that no skeletal rearrangement had occurred during the diazonium ion decomposition.

Catalytic reduction of selaginol gave tetrahydroselaginol which on treatment with phenyl phosphonic dichloride yielded a dichloro compound. The dichloro-compound was converted by catalytic reduction to an oily product containing, as shown by its ultraviolet and N. M. R. spectra, a 2,3 disubstituted pyridine ring. It was thus shown that selagine contains a 5,6 disubstituted α-pyridone ring. Tetrahydroselaginol failed to oxidize with chromium trioxide or to acetylate in boiling acetic anhydride-sodium acetate. On the basis of these observations it was concluded that it is a tertiary alcohol. However, treatment of selaginol with concentrated hydrochloric acid yielded a ketone in which the chromophore depicted below was shown to be present.



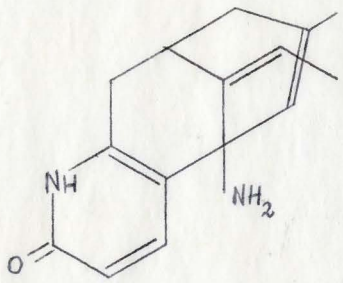

The rearrangement involved in the reaction of selaginol with concentrated hydrochloric acid was formulated as indicated in Q and thus was established the relationship between the α-pyridone group, the primary amino group and one of the two isolated double bonds.




Q

Dehydrogenation of selagine with palladium on charcoal at 300° C yielded 6-methyl-2-pyridone while dehydrogenation with selenium at 320° yielded an oily base characterized as a crystalline picrate. They proposed that the base obtained on selenium dehydrogenation could well be, on the basis of its analysis and ultraviolet spectrum, 5,7 dimethyl-1-azaanthracene.

The chemical data cited above in conjunction with the biogenetic possibility suggested by Conroy (36) led Wiesner to propose structure R for selagine.



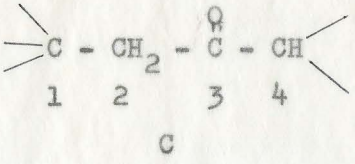

R

Later (45) tetrahydroseloginol was oxidized with $NaIO_4$-$KMnO_4$ to give 2-ethyl-3-carboxyl-5-methyl-cyclohexanone, a result compatible with structure R.

## DISCUSSION OF RESULTS

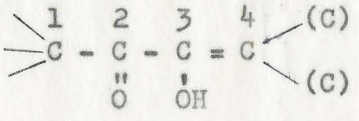
### I Ozonolysis of compound XXI

When this investigation was undertaken it seemed very probable that C depicted the structure of lycopodine in the neighbourhood of the carbonyl group.

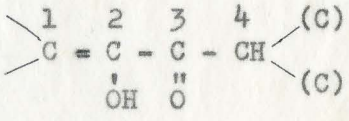


It was known with certainty that a methylene group was present next to the carbonyl function. Carbon atom 4 was believed to be tertiary on the basis of the observation that a compound, very probably bearing a hydroxyl at C-4, was found resistant to oxidation; the N-methyl-tertiary base $C_{24}H_{33}O_2N$, formally derived from the hydroxy-benzylidene compound XXI by substituting the -CN group with $-CH_3$, failed to oxidize (27) by the Oppenauer method. However, Carson's deuterium exchange experiment had not yet been performed and the nature of carbon atom 4 was not known at that time, with certainty.

Partial structures $XVII_a$ and $XVII_b$, for the enolic compound XVII (or XIX) appeared almost equally probable.



$XVII_a$



$XVII_b$

Harrison (23) subjected the enol XVII to oxidation with several reagents hoping to obtain information pertaining to the substituents on C-1. Carbon atom 1, for example, might carry--and this seemed reasonable

by considering the structure of annotinine--the sole methyl group present in lycopodine. If this were the case and partial structure $XVII_b$ were correct, oxidation of the enol would introduce a carbonyl group at C-1 and the product might be expected to give a positive iodoform test. Ozonolysis of compound XVII as well as chromic acid oxidation failed to furnish any crystalline product. Oxidation, however, with potassium permanganate yielded a crystalline diketo acid XXXIV, $C_{17}H_{24}O_4N_2$. Attempts to decarboxylate the diketo acid XXXIV failed to give any compound that could be characterized.

The enol XVII at this stage failed to prove useful in extending the knowledge of the structure of the carbonyl ring. Another compound had to be sought for. Barclay had reported, as described in the previous chapter, that the benzylidene compound XVIII gave two products XXI and XXII when oxidized with selenium dioxide. One, XXI, was a hydroxy compound with the hydroxyl group very probably placed next to the carbonyl, while the other XXII contained an olefinic double bond. It was thought probable that ozonolysis of compound XXI might yield a diketone with enolic properties. In such an enolic diketone the enolic double bond would necessarily be located between C-1 and C-2. An access to C-1 was thus anticipated.

In the first ozonization experiment, hydrogenation over platinum oxide was used to decompose the ozonide. The product obtained was enol XVII. Obviously, during the ozonide decomposition, the hydroxyl group underwent hydrogenolysis. In a subsequent experiment, ozonolysis of XXI was followed by steam distillation which decomposed the ozonide and removed the volatile oxidation products. Two non-volatile products were obtained. One was a neutral yellow compound XXXV, which analyzed well

for $C_{17}H_{24}O_3N_2$, while the other, obtained in lower yield, was an acidic compound XXXVI, $C_{17}H_{24}O_4N_2$.

Hydrogenation of XXXV over platinum oxide yielded the enol XVII. It was thus concluded that compound XXXV was derived from XVII by replacing the hydrogen atom at C-4 by a hydroxyl group. It was, in other words, the diketo alcohol expected to be obtained on ozonolysis of XXI. Compound XXXV, however, had no enolic properties.

The infrared spectrum of compound XXXV in chloroform solution had an intense band at 1724 $cm^{-1}$ which can be definitely assigned to the carbonyl group absorption of an α-diketone. It has been found (46) that a small frequency rise is to be expected in the carbonyl stretching vibration of α-diketones. No bands were present in the conjugated carbonyl and olefinic double bond regions. The ultraviolet spectrum of the enol XVII showed an intense band ($\epsilon$ = 10,000) at 280mμ. Compound XXXV does not absorb strongly at this wave length exhibiting instead maximum absorption at 420mμ($\epsilon$ = 25).

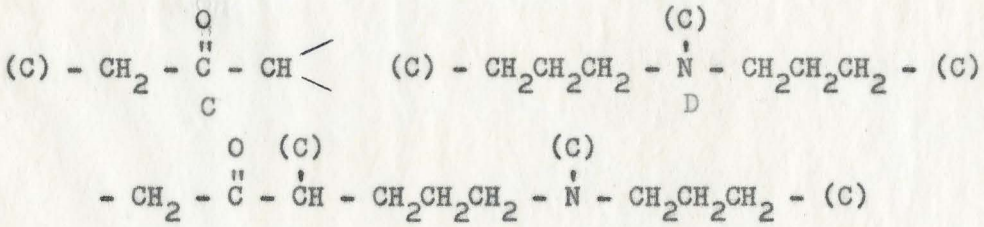
The ultraviolet spectrum of the hydroxy diketone XXXV did not alter in the presence of sodium hydroxide. This fact shows that enolization of this compound is not possible even in the presence of alkali.

The lack of enolic properties of compound XXXV prevented us from carrying out the reactions which were initially planned for the purpose of obtaining information on the structure at C-1. Fortunately, however, this very inability of the diketo alcohol XXXV to enolize furnished us with valuable information on the environment at C-1. In compound XXXV, as was previously pointed out, a hydroxyl group has replaced the hydrogen at C-4 of the enol XVII. The lack of enolic pro-

perties of compound XXXV showed that the hydrogen replaced is the only one available for enolization in XVII. Carbon atom 1, therefore, is either quaternary or at a bridgehead where enolization would be in violation of Bredt's rule.

All this argument pertaining to the structure at C-1 is based on the assumption that the hydroxyl group in compound XXI is placed at C-4. This assignment, as we have already seen, was made on the basis of spectral evidence. Its correctness was established by Carson's deuterium exchange study. It was found by means of this study that the carbonyl group of lycopodine is flanked by three enolizable hydrogens. Two are accounted for by the hydrogens of the methylene group already known to be present next to the carbonyl function. The third enolizable hydrogen must be attached to C-4. If the hydroxyl group in XXXV was not placed at C-4 enolization involving this hydrogen atom would certainly occur.

The combination of partial structures C and D to give E is now unambiguous.



E

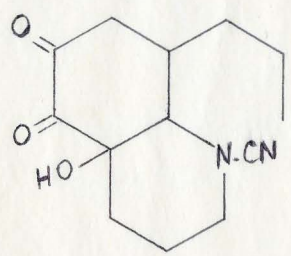
In the preceding chapter it was pointed out that it was possible that the third methylene group in the direction of the 'β' cleavage was identical with the methylene group adjacent to the carbonyl function. This possibility can be now excluded for it implies (taking in account

the deductions on the nature of C-1) the unacceptable conclusion that the second atom from the nitrogen is either quaternary or at a bridgehead.

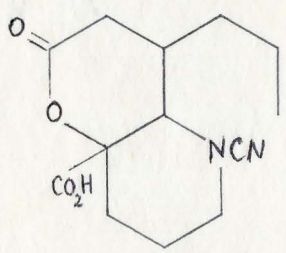
II. A study of compound XXXVI

Compound XXXV was not the only product isolated from the ozonolysis of XXI. An acidic compound XXXVI, which analyzed for $C_{17}H_{24}O_4N_2$, was also obtained. Determination of the neutralization equivalent of XXXVI showed that it was monocarboxylic. Its infrared spectrum showed bands at 1740 and 1680 $cm^{-1}$, as well as nitrile absorption at 2200 $cm^{-1}$. The peak at 1740 $cm^{-1}$ is attributed (47) to the carbonyl group of a $\delta$-lactone. Absorption at 1680 $cm^{-1}$ can be assigned to the carboxylic group.

On adopting the hexahydrojulolidine formulation B the partial structures shown below can be assigned to compounds XXXV and XXXVI.

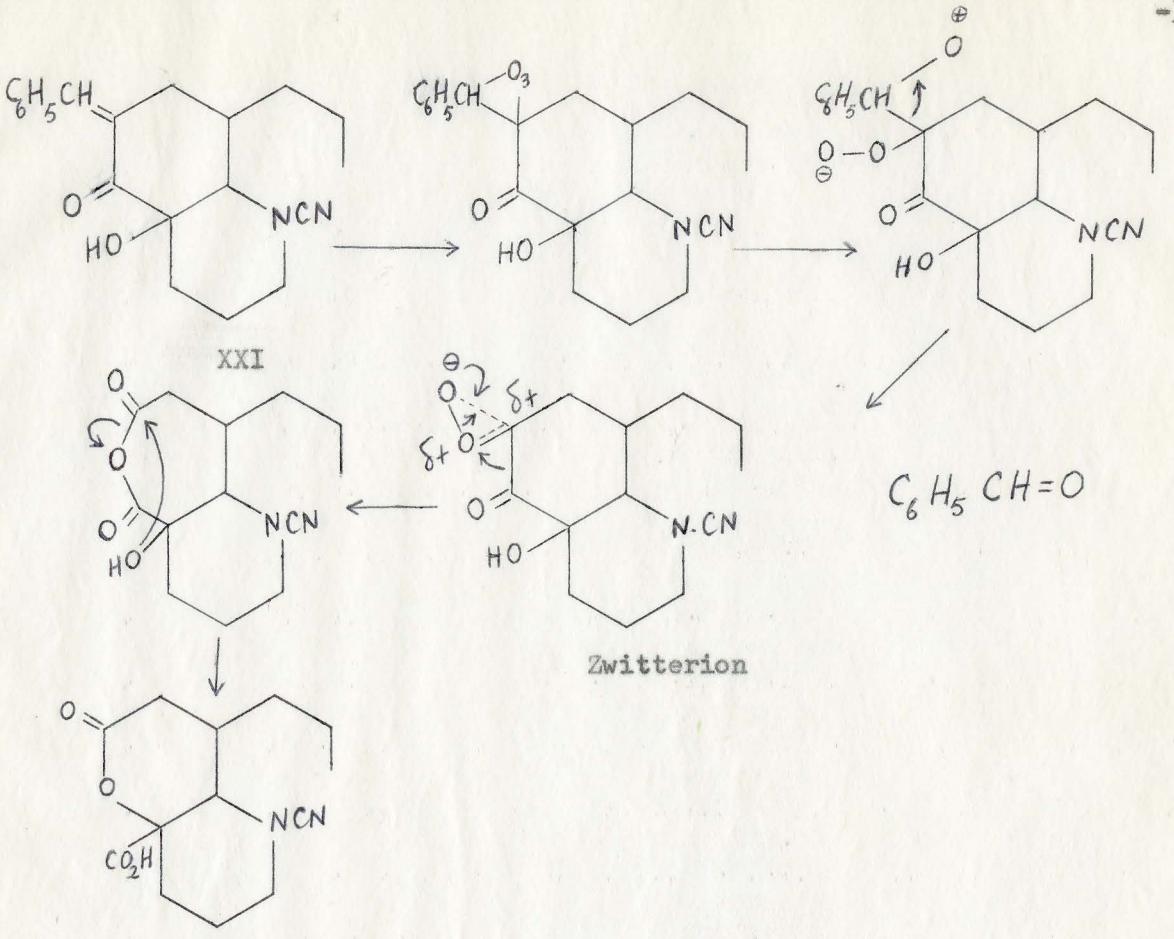



XXXV




XXXVI

The mechanism formulated below is proposed for the formation of compound XXXVI.




The formation of a zwitterion intermediate by the steps shown has been postulated by Criegee (48-52) for the reaction of ozone with olefins. The zwitterion gives a hydroxy-anhydride which in turn is converted to the lactone-carboxylic acid XXXVI. The postulation of an anhydride intermediate is supported by the following facts:

(i) A cyclic anhydride XX was obtained by Barclay when the benzylidene compound XVIII was ozonized in ethyl acetate solution.

(ii) Transformations by ozonolysis of α,β-unsaturated ketones to products which can be accounted for by the mechanism leading to the anhydride (step 4) have been reported in the literature (53). Fig. 4 summarizes the reactions discussed to this point.

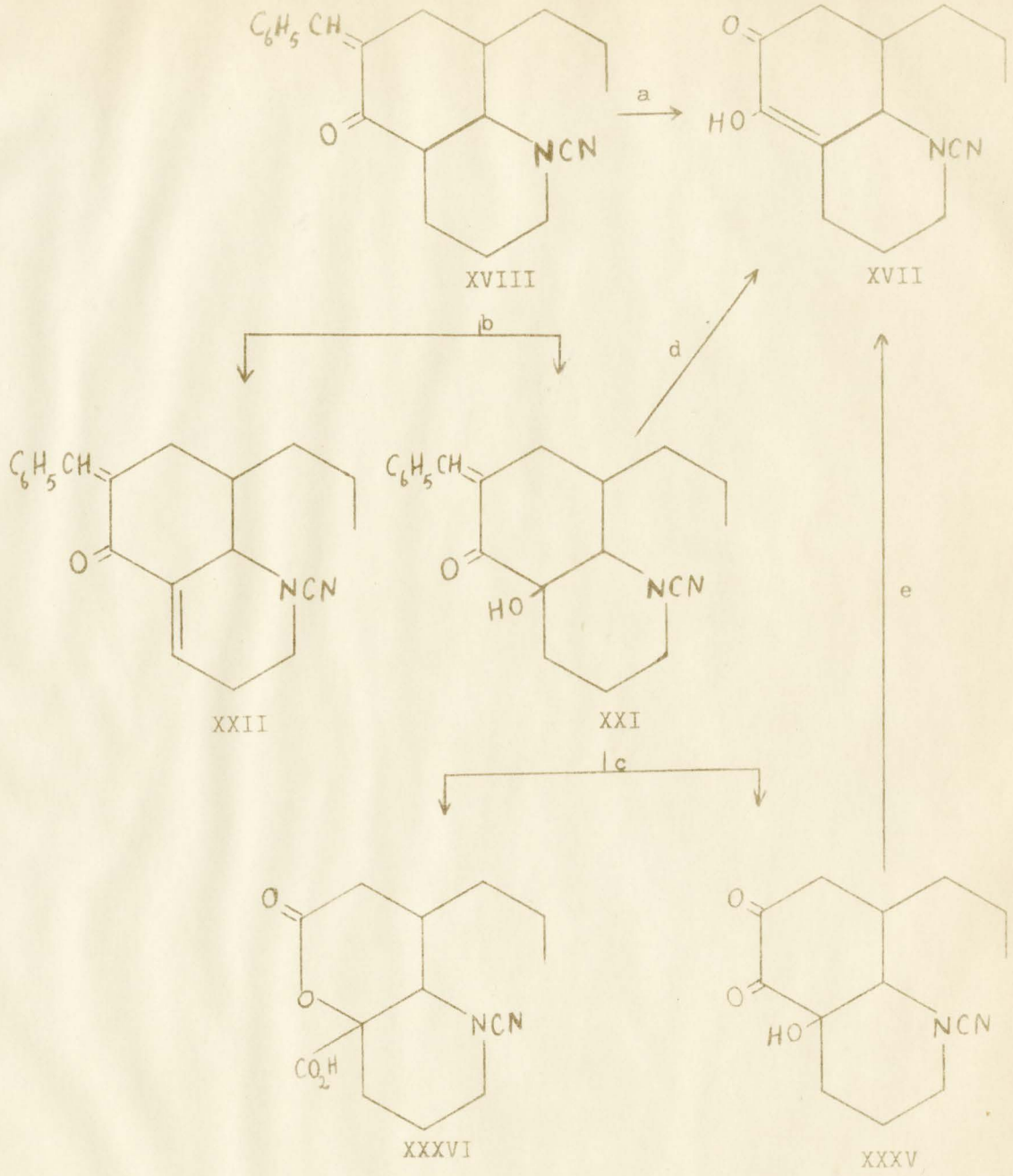



Fig. 4

a. $O_3$

b. $SeO_2$

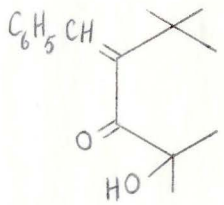
c. 1. $O_3$
2. $H_2O$

d. 1. $O_3$
2. $H_2$, $PtO_2$

e. $H_2$, $PtO_2$

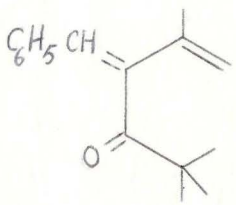
III A study of the olefinic compound XXII.

As has already been stated, it is possible, on the basis of the ozonization experiments conducted by the author and Carson's deuterium exchange studies, to assign with certainty partial structure $XXI_a$ to the hydroxy-benzylidene compound XXI.



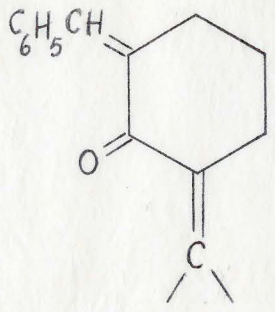

$XXI_a$

A study was now made of the olefinic compound XXII, the other product obtained on oxidation of compound XVIII with selenium dioxide. Partial structure $XXII_b$ can be definitely excluded for it has been




$XXII_b$

proved that C-1 in compound XVIII is either quaternary or at a bridge-head. The alternative structure $XXII_a$ seemed almost with certainty to be correct.



$XXII_a$

However, no evidence was at hand excluding a rearrangement of the carbon skeleton when XXII was formed. Such evidence has now been obtained. The benzylidene compound XVIII was hydrogenated in the presence of platinum oxide to compound XXXVII, $C_{24}H_{32}ON_2$. The same product, XXXVII was obtained on catalytic hydrogenation of compound XXII. The latter, therefore must have the same carbon skeleton as the benzylidene derivative XVIII.

The N. M. R. spectrum of compound XXII, shown in fig. 5 is in agreement with structure $XXII_a$. A triplet peak occurring at a displacement of $\tau = 2.92$ can be assigned to the olefinic proton. Such an assignment is in agreement with the low chemical shifts attributed in previous work (32, 54) to protons on the β-carbon of α,β-unsaturated carbonyl compounds. The intense peak with a chemical shift of 2.61 is attributed to the phenyl group protons while the peak with $\tau = 2.25$ can be assigned to the proton of the methene group attached to the aromatic ring.

IV. The total structure of lycopodine

The evidence has already been presented which enabled us to

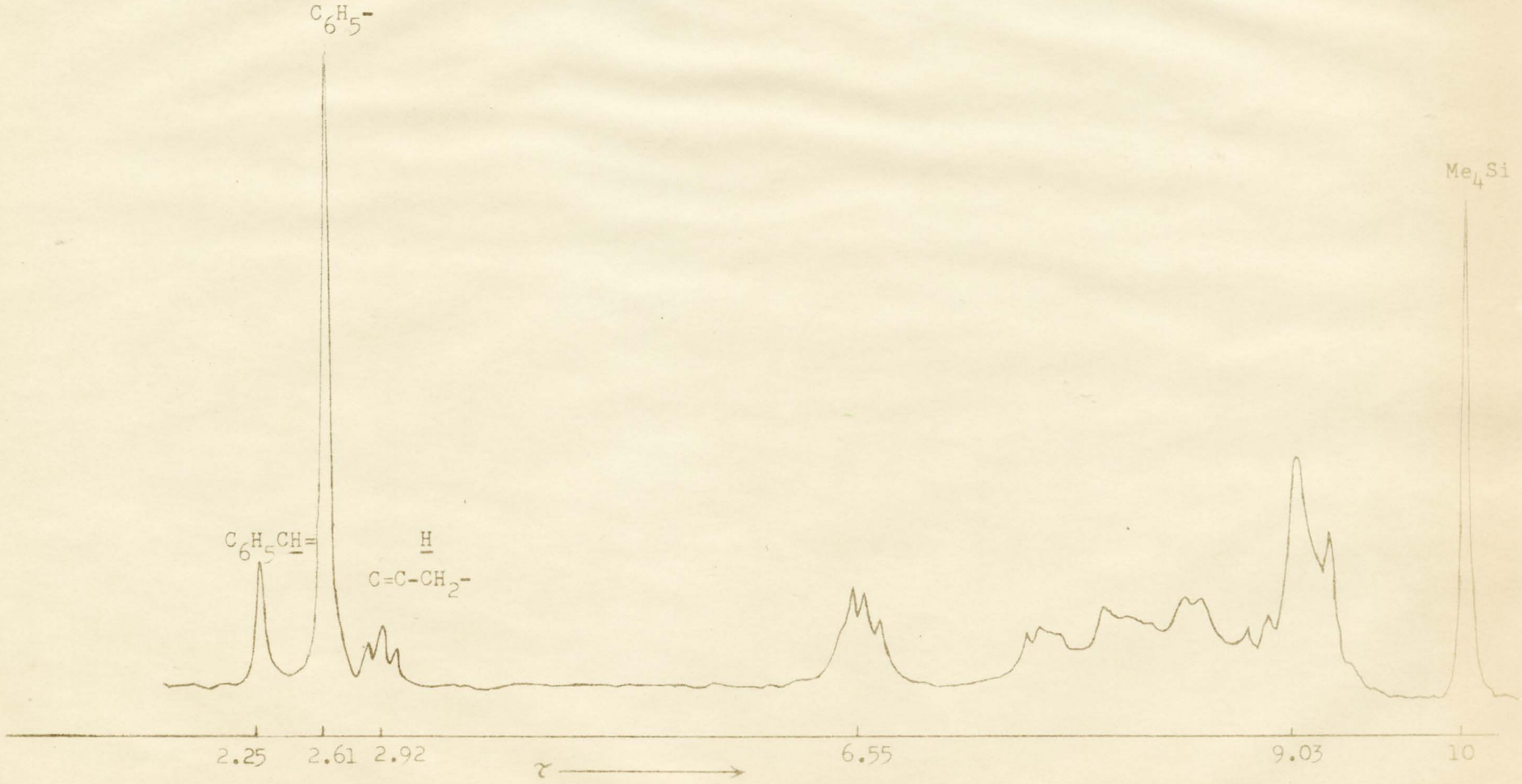
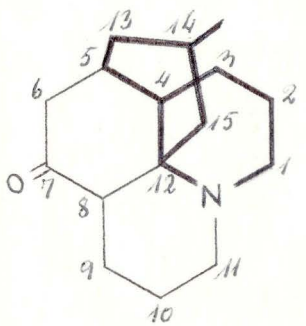



Fig. 5 The N.M.R. Spectrum of compound XXII

exclude the possibility that the carbonyl group was located at the fourth carbon atom from the nitrogen in the direction of the 'β' cleavage. Partial structure E was established with certainty to be present in the alkaloid molecule. The possibility of the presence of a hexahydrojulolidine ring system was thus enhanced.

A consideration of the dehydrogenation experiments of Marion and Manske (6) made possible the proposal (22) of a total structure for lycopodine. It will be recalled that lycopodine on dehydrogenation yielded 7-methyl-quinoline and 5:7-dimethyl-quinoline as well as three other basic products which were not characterized.

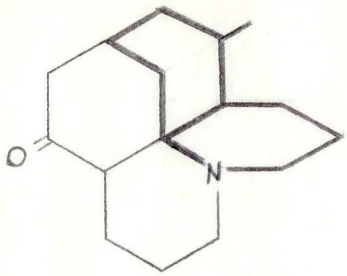
Total structure S is consistent with the dehydrogenation results and with all the reactions of the alkaloid and its derivatives.




S

The decahydro-quinoline nucleus which would give rise to the two quinoline derivatives is marked by a heavy line.

One more structure for lycopodine could be written which was consistent with its chemistry and could account for the dehydrogenation results. This is the non-hexahydrojulolidine structure T.



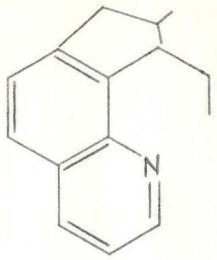

T

Structure T is less attractive than S since it might be expected to furnish 5-methyl-quinoline, as a major product, on dehydrogenation.

V. Dehydrogenation experiments

Barclay (27) reported that dehydrogenation of base XXIII gave in small yield a product which on the basis of its ultraviolet spectrum, appeared to be an alkylated quinoline. In a subsequent experiment (55) he dehydrogenated a base obtained from XXIII by dehydration. The product, which had also the properties of an alkylated quinoline, contained all the carbon atoms of the lycopodine molecule.

The quinoline nucleus from which the dehydrogenation products might arise is composed from rings B and C in structures S and T. Identification of these compounds would have enabled the choice between structures S and T. If it were established that the quinoline nucleus in the dehydrogenation products was alkylated at C-7 and C-8 one would adopt structure S. If it were alkylated at C-7 only, structure T would have been preferred. The failure to identify the dehydrogenation products was due to the fact that alkylated quinolines with relatively large alkyl groups, as the one shown below, were not described in the literature.




7:8-Dimethyl-quinoline and 7-methyl-quinoline, however, have been characterized. It was desirable, therefore, to find those dehydrogenation conditions under which the side chains would be degraded to methyl groups. Dehydrogenation under such conditions would yield 7:8-dimethyl-quinoline if structure S was correct while 7-methyl-quinoline would be expected to form if T represented the structure of lycopodine. A high temperature dehydrogenation in the vapour phase using a noble metal catalyst was considered promising for this purpose. Accordingly, compound XXXVIII, derived from α-cyanohydroxylycopodine VI by reduction of the carbonyl group, was subjected to dehydrogenation but the products obtained could not be characterized. The dehydrogenation of XXXVIII thus failed to furnish the desired information.

It was felt that it was worth while to attempt the dehydrogenation of the secondary base corresponding to XXXVIII. Accordingly the diol XXXVIII was hydrolyzed in an aqueous alcoholic solution of hydrochloric acid. The non-crystalline base XXXIX obtained was converted to a crystalline perchlorate XL. The analytical figures of compound XL were in agreement with the formula $C_{16}H_{28}O_5NCl$. Evidently the removal of the nitrile group was accompanied by dehydration. This is not surprising since it had been found (56) in this laboratory that dihydrolycopodine II dehydrated readily when treated with mineral acid. Compound XXXIX was subjected to dehydrogenation but again, however, it was not pos-

sible to characterize the fractions obtained from the crude reaction product.

At this time Anet reported (37) the transformation of annofoline (structure G) to anhydrolycopodine XIV. It had been previously shown (35) that in annofoline ring D contains the grouping $-\overset{O}{\overset{\|}{C}}-\overset{H}{C}HCH_3-CH_2-$. A structure analogous to T can be therefore excluded for this alkaloid. The transformation of annofoline to anhydrolycopodine thus established the correctness of structure S and to pursue further the dehydrogenation experiments was pointless. Anet's transformation also established the stereochemistry at C-14. It was shown that the configuration at C-14 is the same as in deacetyl-fawcettiine which is involved in the transformation sequence. The reactions carried out by Anet are formulated in fig. 6.

The configuration at C-4 is revealed from the formation of the cyclized compound IX. The ring closed on formation of compound IX can not be on the same side of the molecule as ring D. This can be readily seen by inspecting molecular models. Therefore, it can be concluded with certainty that the hydrogen at C-4 is cis to ring D.

VI. An attempt to determine the configuration at C-8

The only feature left to be determined in the study of the relative stereochemistry of lycopodine was the configuration at C-8. Structures U and V may be written placing the hydrogen at C-8 cis to ring D. Of the two structures V appeared to be more favorable.

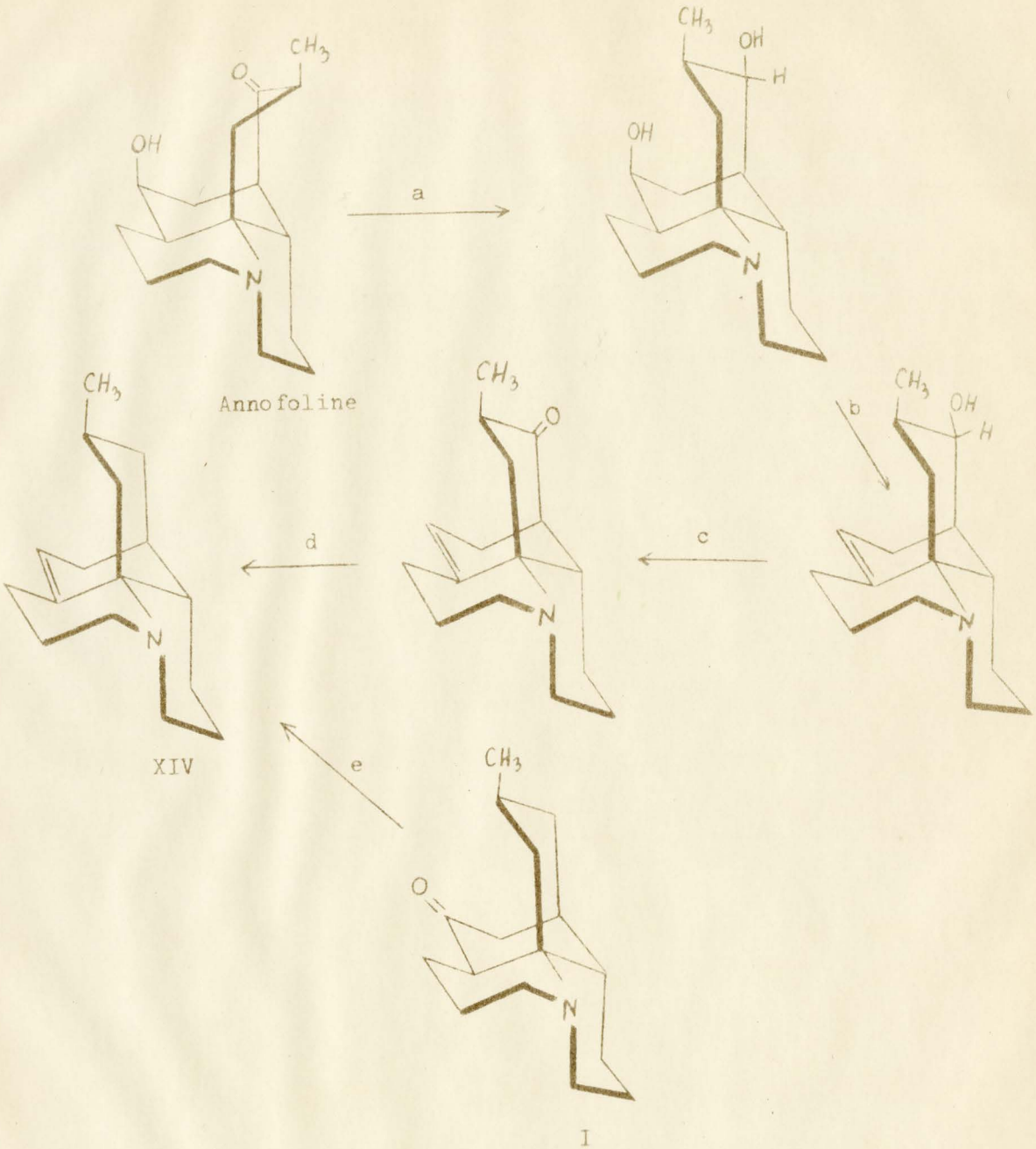



Fig. 6

a. $NaBH_4$, NaOH

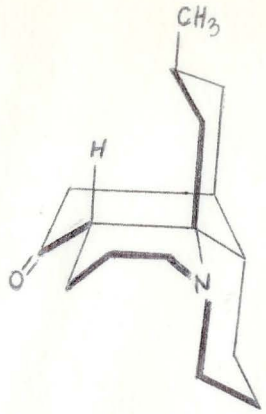
b. $SOCl_2$

c. $CrO_3$

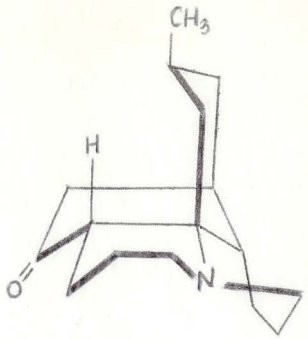
d. $N_2H_4$, NaOH

e. 1. $LiAlH_4$

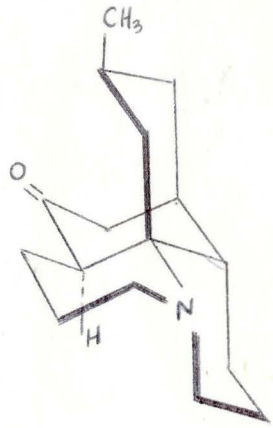
2. $SOCl_2$




U




V




W

In structure U a large repulsive energy term arises from the proximity of the axial hydrogens at C-1 and C-9. Structure W in which there is a trans relationship between the hydrogen at C-8 and ring D, appeared to be, on examining molecular models, more stable than any other conceivable structure.

An attempt was made to establish definitely the configuration of lycopodine at C-8. The experiments which are discussed hereafter were planned with this goal in mind.

Harrison (23) carried out a von Braun reaction on acetyldihydrolycopodine XV. The crude product was then treated with potassium acetate. The diacetates formed were hydrolyzed with potassium hydroxide to give a mixture of the isomeric diols XXXVIII and XLI which were subsequently separated. The reactions involved are shown in fig. 7.

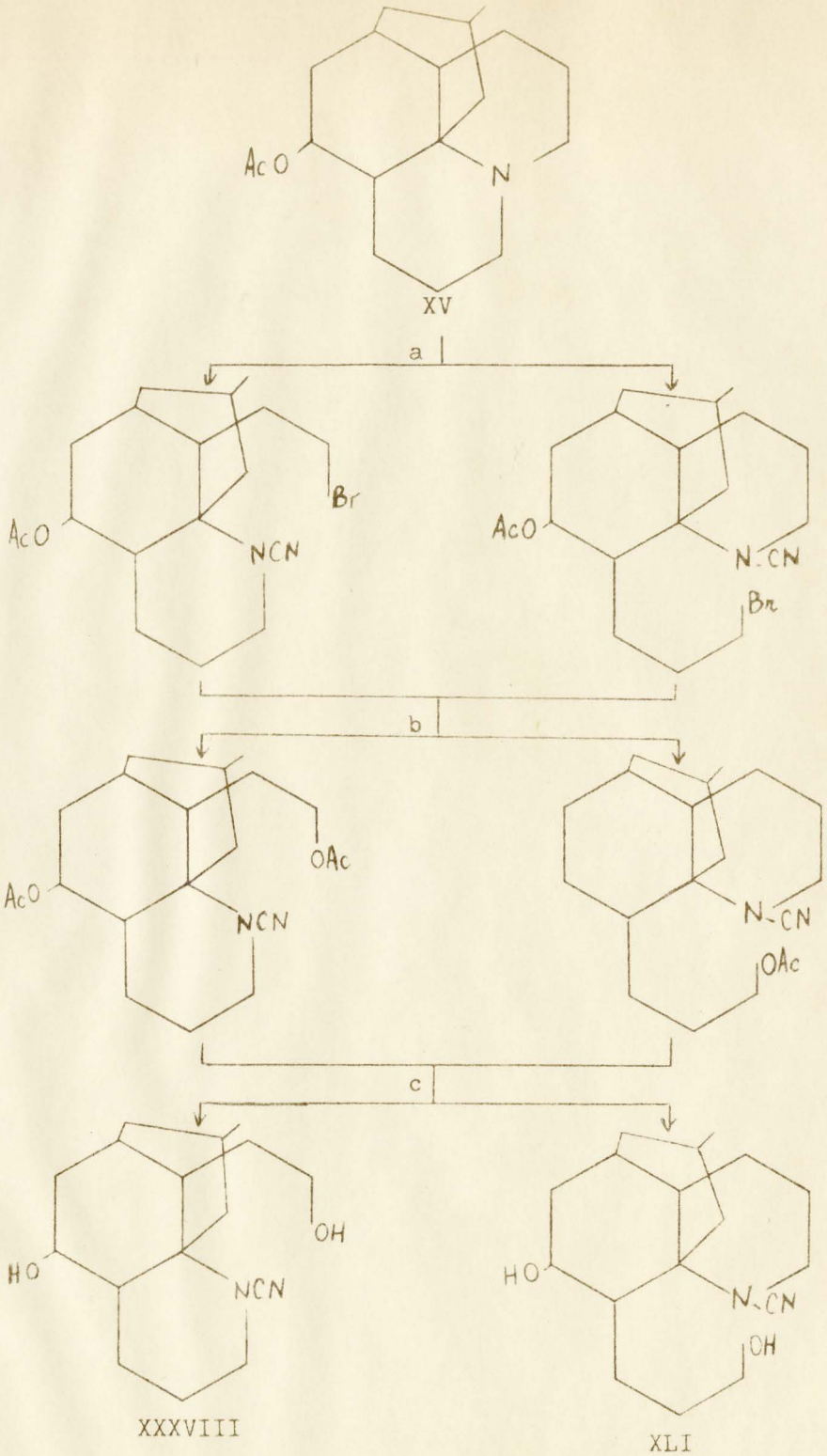



Fig. 7

a. CNBr

b. AcOK in boiling EtOH

c. KOH in boiling MeOH

In the sequence of reactions, above, an inversion at C-8 can be excluded. Inversion could only occur in the presence of a carbonyl group at C-7. It can be concluded, therefore, that compound XXXVIII (as well as XLI) has the same configuration at C-8 as lycopodine. As was mentioned earlier the diol XXXVIII was also obtained by the following transformations: Lycopodine I on being treated with cyanogen bromide gave α-cyanobromide III which by the action of potassium acetate yielded α-cyanoacetoxy-lycopodine V. Compound V was hydrolyzed with potassium hydroxide to give α-cyanohydroxylycopodine VI. Sodium borohydride reduction of compound VI gave XXXVIII. Compound VI was obtained in alkaline medium. It has, therefore the most stable configuration at C-8. It is very reasonable, then, to assume that the step VI → XXXVIII does not involve inversion. α-Cyanohydroxylycopodine VI has, therefore, the same configuration at C-8 as the diol XXXVIII. Taking into account Harrison's transformation, discussed previously, we can conclude that compound VI and lycopodine I have the same configuration at C-8.

α-Cyanohydroxylycopodine VI can formally be derived from α-cyanolycopodine XII by replacing a terminal hydrogen atom of the n-propyl group present by a hydroxyl group. This change has obviously no effect in the vicinity of carbon atom 8. Therefore, it can be concluded that the stable epimer at C-8 of α-cyanolycopodine is that with the same configuration at this center as compound VI or lycopodine. α-Cyanolycopodine XII on being refluxed with alkali did not epimerize and is therefore the more stable of the epimeric α-cyanolycopodines. We have thus arrived at the conclusion that α-cyanolycopodine XII has the same configuration at C-8 as lycopodine. Our problem is thus

reduced in establishing the configuration at C-8 of α-cyanolycopodine.

It has been stated in another section that both the benzylidene compound XVIII and the olefinic benzylidene compound XXII give the same product XXXVII on catalytic hydrogenation. In the catalytic hydrogenation of compound XXII one would expect the hydrogen to add to the two double bonds from the less hindered side of the molecule, opposite ring D. The hydrogenation product should have the hydrogen at C-8 trans to ring D. It can thus be concluded that compound XXXVII as well as the benzylidene compound XVIII have the C-8 hydrogen in a trans relationship to ring D.

Knowing the stereochemistry of the benzylidene compound XVIII, the next thing to be done was to attempt the transformation of both this compound and α-cyanolycopodine XII to compounds of common skeletal structure by reactions that could not involve epimerization. If the same substance were obtained by both paths it could be concluded that α-cyanolycopodine XII and therefore lycopodine itself have the same configuration at C-8 as the benzylidene compound XVIII i.e., the hydrogen at C-8 and ring D in a trans relationship. If on the other hand the two reaction sequences led to epimers it would be concluded that the benzylidene compound XVIII and α-cyanolycopodine have different configurations at C-8. Lycopodine in that case would have the hydrogen at C-8 on the same side of the molecule as ring D.

The reactions shown in fig. 8 were designed for the purpose of establishing the stereochemistry of lycopodine at C-8.

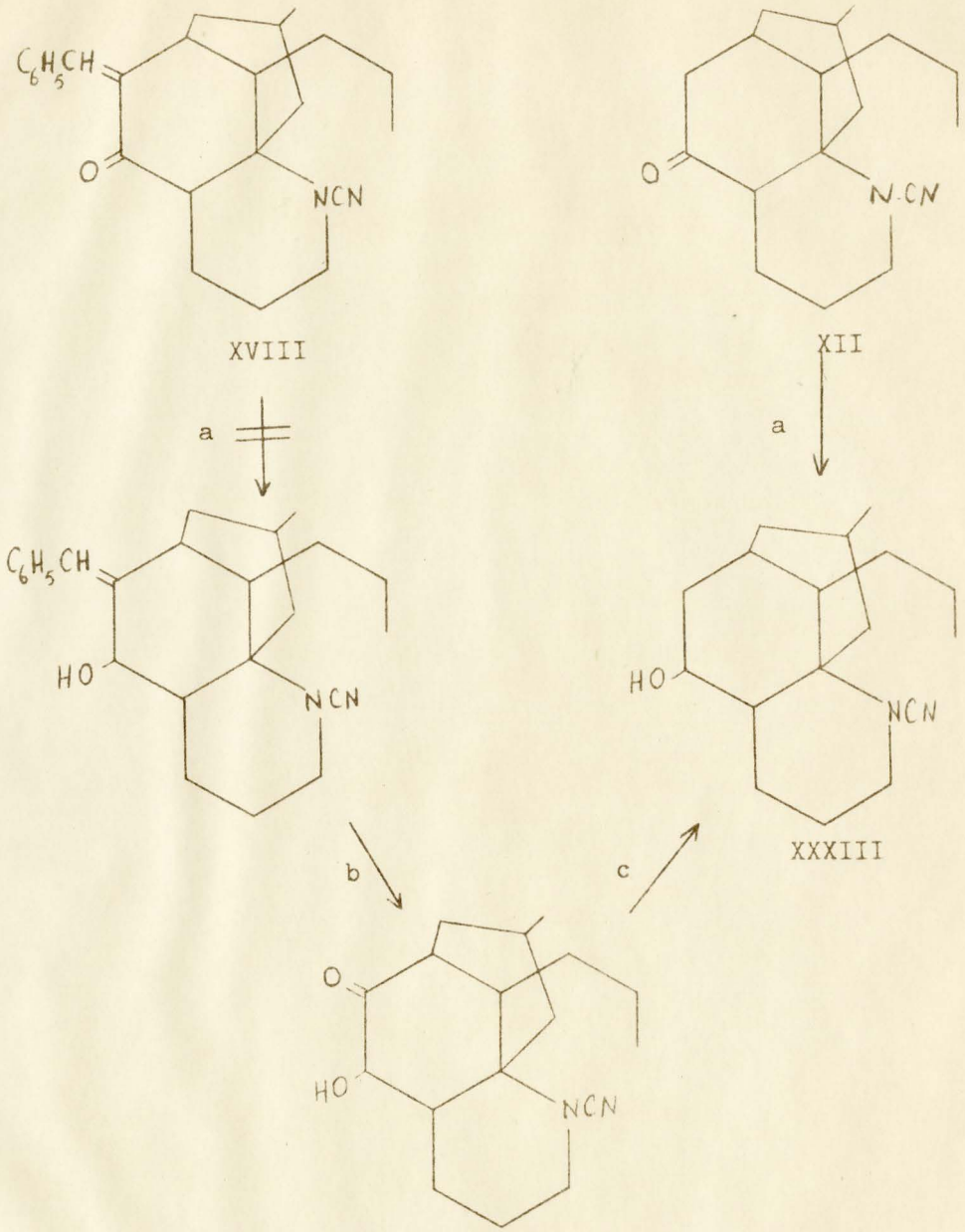



Fig. 8

a. $NaBH_4$

b. $O_3$

c. $N_2H_4$, NaOH

Sodium borohydride reduction of XVIII, the first step in the transformations of the benzylidene compound, did not proceed as expected. Instead of the anticipated dihydrobenzylidene derivative compound, XLII was obtained, in which both the carbonyl, and olefinic double bonds were reduced. This was not realized at the time and compound XLII was subjected to ozonolysis. The product obtained analyzed well for $C_{24}H_{32}ON_2$. It was found by a mixed melting point determination to be identical with compound XXXVII, previously obtained by catalytic hydrogenation of compounds XVIII and XXII. This result turned our attention to compound XLII. Its ultraviolet spectrum had λmax at 260mμ ($\epsilon$ = 380). This indicated the absence of a conjugated olefinic double bond in the molecule. Finally XLII was obtained by sodium borohydride reduction of XXXVII.

The reactions involved are summarized in fig. 9.

The failure to carry out the scheme outlined in fig. 9 did not permit an unambiguous assignment of configuration at C-8. However, it is probable that both α-cyanolycopodine and the benzylidene compound have in their most stable configuration the same stereochemistry at C-8. It has been shown that the benzylidene compound XVIII, which is in the most stable configuration (having been formed in alkaline medium), has the C-8 hydrogen trans to ring D. Hence α-cyanolycopodine XII also existing in the most stable form, very probably has the same configuration at C-8 with the benzylidene compound XVIII.

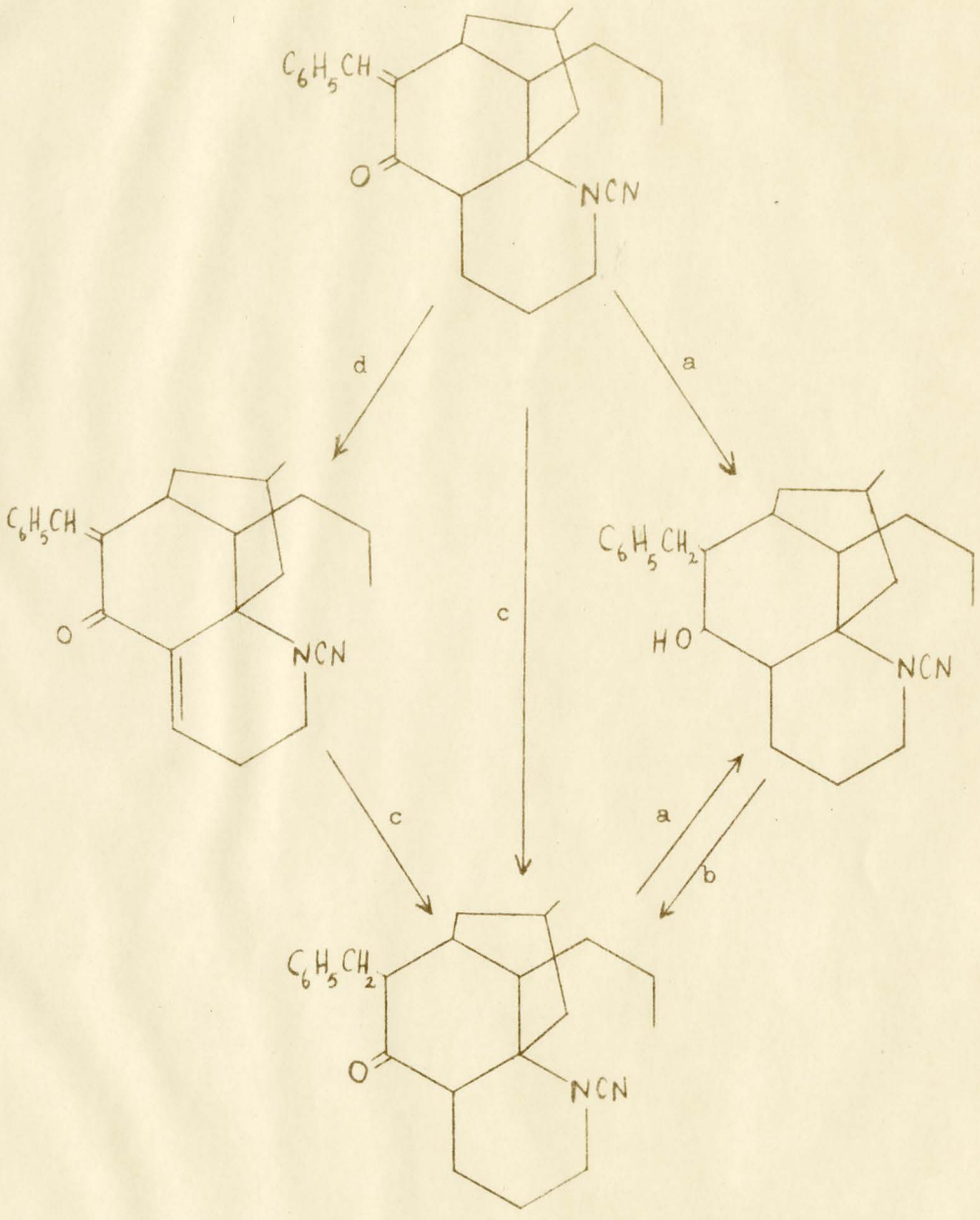



Fig. 9

a. $NaBH_4$

b. $O_3$ in MeOH

c. $H_2$, $PtO_2$

d. $SeO_2$

## EXPERIMENTAL

Infrared spectra were determined using a Perkin-Elmer Model 21B double beam infrared recording spectrophotometer. Samples were mounted in nujol except where otherwise stated. Ultraviolet spectra were determined using a Perkin-Elmer spectrocord 4000.

Nuclear magnetic resonance spectra were measured in deuterochloroform solution using a Varian V-4300B spectrometer equipped with a field stabilizer at a fixed frequency of 56.4 Me/sec. Tetramethylsilane was used as an internal standard.

Analysis of samples were performed by Drs. G. Weiler and F. B. Strauss Oxford, England and E. Thommeu, Basel, Switzerland.

### Isolation of lycopodine

The plant species Lycopodium flabelliforme was used as a source of lycopodine. The dry, ground plant material was extracted by the method of Manske and Marion (5). Lycopodine was separated from the crude alkaloid extract by chromatography on alumina using benzene as the eluant. Lycopodine passed through the alumina column rapidly and was thus separated from other alkaloid constituents. Crystallization of lycopodine was effected from an ether solution (m.p. 115.5-116°).

### Reaction of lycopodine with cyanogen bromide.

Cyanogen bromide (90g) was dissolved in 200 ml. of benzene. The solution was distilled over calcium chloride. The distillate was dried over drierite and decanted into the reaction flask. A dried solution of lycopodine (23g) in benzene (160 ml.) was added to the stirred solution of cyanogen bromide over a period of 5 hours. The

reaction mixture was then allowed to stand overnight. The benzene and excess cyanogen bromide were removed under reduced pressure on a water bath, keeping the temperature of the mixture below 60° C. The residue was dissolved in benzene and washed with water, dilute hydrochloric acid and dilute bicarbonate solution. From the acid washings 2g of unreacted lycopodine were recovered. The benzene solution was dried over sodium sulphate, concentrated and adsorbed on a column of alumina. Elution with benzene yielded a fraction from which a mixture of bromocyanamides III and IV was obtained. Fractional crystallization from ether yielded in total 10.8g of α-cyanobromolycopodine III and 2g of β-cyanobromolycopodine IV. A mixture (2.6g) of the two cyanobromides which was not separated into its components was also obtained.

Preparation of α-cyanolycopodine XII

α-Cyanobromolycopodine III (8.2g) and sodium hydroxide (2.8g) were dissolved in approximately 130 ml of methanol. 1.9g of 5% palladium-calcium carbonate catalyst were added to the solution. The mixture was shaken with hydrogen at 40 lb./sq. in. for 8 hours and then filtered. The residue from evaporation of the filtrate was treated with water and extracted several times with ether. The ether solution was dried over anhydrous sodium sulphate and filtered. On concentrating the solution crystallization occured. Recrystallization yielded 5.1g of α-cyanolycopodine XII (m.p. 130-131°).

Preparation of the benzylidene compound XVIII

α-Cyanolycopodine XII (5.6g) and purified benzaldehyde (4.2g) were dissolved in absolute methanol in a flask equipped with a dropping funnel and reflux condenser. A solution (23 ml) of sodium methoxide in

absolute methanol, prepared from 6g of sodium and 75 ml of methanol, was added dropwise to the refluxing solution over a period of 15 minutes. The reaction mixture, was allowed to stand overnight at room temperature. It was then taken to dryness. The residue thus obtained was dissolved in chloroform. The chloroform solution was washed several times with water and then dried over sodium sulphate. Evaporation of the solvent under reduced pressure yielded a viscous liquid residue. The residue was dissolved in methanol and the methanol solution concentrated. The benzylidene compound XVIII (3.9g) melting at 179.5-180.5° was obtained.

Selenium dioxide oxidation of compound XVIII

Selenium dioxide (1.8g) was added to a solution of 2.8g of the benzylidene compound XVIII in approximately 100 ml of dioxane. The mixture was heated under reflux for 3 hours and was then allowed to stand overnight at room temperature. The residue obtained after the evaporation of the solvent was exhaustively extracted with ether. The ether solution thus obtained was washed with water, dried over sodium sulphate and concentrated to a small volume. On cooling, crystallization occured furnishing 1.8g of the hydroxy-benzylidene compound XXI (m.p. 212-217°). The mother liquors were treated with methanol. Crystallization from a methanol-ether solvent system furnished 0.5g of compound XXII (m.p. 199-202°).

Ozonolysis of the hydroxy-benzylidene compound XXI

(Decomposition of the ozonide by catalytic hydrogenation).

A solution of 0.2g of compound XXI in 30 ml of 1:1 methanol-acetic acid was ozonized by passing through the solution a stream of oxygen containing approximately 5% ozone at a rate of 50 ml/min. for

25 min. The temperature was maintained at -15°. The solution was then treated with hydrogen (under a pressure of 26 lb/sq. in.) for two hours in the presence of a platinum oxide catalyst. The catalyst was filtered off and the solution evaporated to dryness under reduced pressure. The residue obtained was dissolved in ether and washed with dilute bicarbonate solution and subsequently with dilute hydrochloric acid. The ether solution was then exhaustively extracted with dilute sodium hydroxide solution. The last extract was made acidic by the addition of dilute hydrochloric acid and extracted with chloroform. The chloroform solution was taken to dryness and the residue was dissolved in a small volume of ether. Crystallization from this solvent furnished 0.14g of a substance (m.p. 157-158°) which was found, by a mixed melting point determination, to be identical with the enolic compound XVII.

Ozonolysis of the hydroxy-benzylidene compound XXI

(Decomposition of the ozonide with water).

Compound XXI (0.36g) was dissolved in 20 ml of methanol and 15 ml of acetic acid. The solution was ozonized for 25 min. at -20°. During this period of time approximately 1 1/2 liters of oxygen containing 5% ozone was bubbled through the solution. The reaction mixture was then transferred into a flask arranged for steam distillation and steam was passed through the solution for a period of about half an hour. Benzaldehyde was detected in the distillate by formation of its 2,4 dinitrophenylhydrazone. The residue from the steam distillation was cooled and a crystalline precipitate separated from the aqueous solution. Recrystallization from ether yielded 0.2g of bright yellow crystals (compound XXXV) which melted at 223-225°.

Calc. for $C_{17}H_{24}O_3N_2$: C, 67.08; H, 7.95; N, 9,20%.

Found: C, 67.05; H, 7.99; N, 8.77%.

The infrared spectrum of compound XXXV in chloroform showed broad hydroxyl absorption at approximately 3300 $cm^{-1}$, cyanamide absorption at 2219 $cm^{-1}$ and a strong carbonyl band at 1724 $cm^{-1}$. The ultraviolet absorption spectrum of compound XXXV showed $\lambda max = 420 m\mu$, $\epsilon = 25$.

The aqueous residue, after removal of the yellow precipitate, was extracted with chloroform. The chloroform solution was then extracted with dilute bicarbonate solution. The aqueous extract was made acid by addition of dilute hydrochloric acid solution and extracted with chloroform. The latter chloroform solution was dried over sodium sulphate, and taken to dryness under reduced pressure. The residue was dissolved in acetone. Ether was added to the acetone solution and crystallization from the acetone-ether mixture furnished a small quantity (0.011g) of compound XXXVI (m.p. 206-208°).

Calc. for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74%.

Found: C, 63, 65; H, 7.71; N, 8.41%.

The infrared spectrum of compound XXXVI showed absorption at 1680 $cm^{-1}$, 1735 $cm^{-1}$ and cyanamide absorption at 2210 $cm^{-1}$. The neutralization equivalent of compound XXXVI was 0.97.

Catalytic hydrogenation of compound XXXV

A solution of 0.1g of compound XXXV in 25 ml of methanol was shaken, in the presence of platinum oxide, with hydrogen (35 lb/sq. in.) for four hours. The solution was then filtered. The residue from the evaporation of the filtrate was dissolved in ether. The ether solution was washed with dilute hydrochloric acid and water. It was then extracted

with dilute aqueous sodium hydroxide solution. The aqueous extract thus obtained was made acid with dilute hydrochloric acid and extracted with chloroform. The chloroform solution was taken to dryness and the residue obtained was dissolved in ether. Crystallization from this solvent furnished 0.05g of a compound whose melting point (159-160°) was not depressed on admixture with an authentic sample of the enol XVII.

Catalytic hydrogenation of compound XVIII

The benzylidene compound XVIII (0.2g) was dissolved in 25 ml of methanol containing 0.1g of platinum oxide. The mixture was shaken with hydrogen at 34 lb/sq. in. for eight hours. After removal of the catalyst by filtration the solution was evaporated to dryness. The crystalline residue was recrystallized from ether and yielded compound XXXVII which melted at 206-208° C.

Catalytic hydrogenation of compound XXII

Compound XXII (0.15g) was dissolved in approximately 65 ml of methanol. Platinum oxide catalyst was added to the solution which was subsequently treated with hydrogen at a pressure of 30 lb/sq. in. for eleven hours. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in ether. On concentrating the ether solution crystallization occured. The product obtained (0.06g) melted at 206-208° and was found, by a mixed melting point determination, to be identical with compound XXXVII obtained by hydrogenation of the benzylidene compound XVIII.

Calc. for $C_{24}H_{32}ON_2$: C, 79.08; H, 8.85; N, 7.69%.

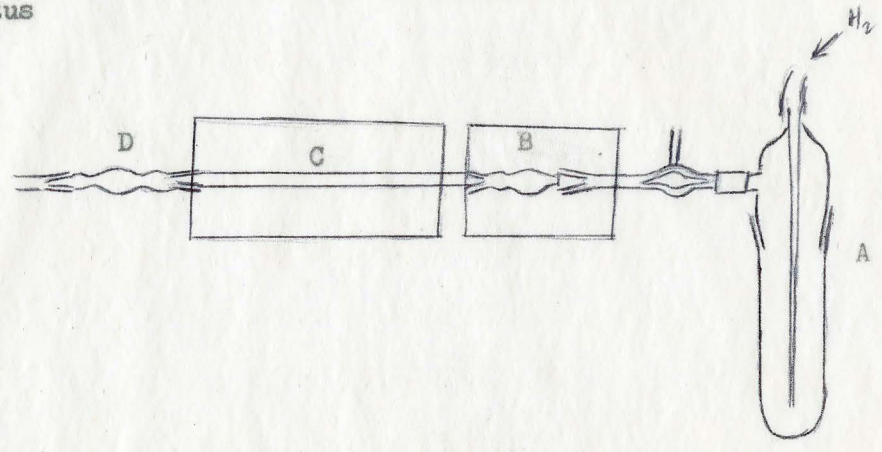
Found: C, 79.15; H, 8.85; N, 7.84%.

The infrared spectrum of compound XXXVII showed carbonyl absorption

at 1697 $cm^{-1}$ as well as cyanamide absorption at 2200 $cm^{-1}$.

Dehydrogenation experiments

A. Apparatus




A brief description is given here of the apparatus used in the dehydrogenation experiments.

A bubbler A, containing sulfuric acid, served to indicate the flow rate of the hydrogen which was passed during the experiment through the system. The substance to be dehydrogenated was placed in tube B. The adjoining tube C was packed with the catalyst. Both compartments B and C were placed in furnaces. By raising sufficiently the temperature in B the substance being studied was vaporized and its vapors were swept by the hydrogen stream through the heated catalyst. The tube D, cooled by a stream of water, was used to collect the reaction product.

B. Catalyst

The catalyst was 30% platinized charcoal prepared according to the method of Linstead (57) under the heading catalyst-d. The catalyst was mixed with an equal weight of asbestos.

C. Gas chromatographic column

The column material used, in the separation of the constituents of the crude dehydrogenation product, was prepared by the following method. Apiezon N (28g) was dissolved in 280 ml of petroleum ether (30-60°) 112g of celite (545, mesh 80-120), washed with 5% methanolic potassium hydroxide, were added to the solution. The solvent was then evaporated under vacuum in a rotary evaporator. The celite-apiezon mixture was dried at 100°.

Dehydrogenation of the diol XXXVIII

Tube B was filled with the diol XXXVIII (0.49g). The temperature was raised in both compartments B and C to approximately 350° and was kept there throughout the experiment. The crude product obtained (0.21g) was dissolved in a small volume of acetone and passed through a gas chromatographic column. Five fractions were obtained. Attempts to convert these fractions to crystalline picrates were unsuccessful.

Treatment of compound XXXVIII with hydrochloric acid

Compound XXXVIII (0.5g) was dissolved in a mixture of 2M hydrochloric acid (20 ml) and n-propanol (5 ml). After refluxing the solution for twelve hours most of the propanol was removed by evaporation and water was added to the residue. The solution was made basic with ammonia and extracted with chloroform. The chloroform solution was extracted with dilute hydrochloric acid solution. The extract was basified with ammonia and extracted with chloroform. The base obtained (compound XXXIX) after removing the chloroform failed to crystallize. It gave however a crystalline perchlorate salt XL which melted at 188-192°.

Calc. for $C_{16}H_{28}O_5NCl$: C, 54.93; H, 8.01; N,4.00%.

Found: C, 55.17; H, 8.17; N, 3.90%.

The infrared spectrum of compound XL showed absorption at 3400 $cm^{-1}$, 3170 $cm^{-1}$ and a strong band at 1625 $cm^{-1}$ due to $NH_2$ deformation.

Dehydrogenation of compound XXXIX

Base XXXIX, obtained from the corresponding perchlorate, was subjected to those dehydrogenation conditions described previously. The product, in a concentrated acetone solution, was subjected to vapor phase chromatography. Five fractions were obtained which failed to form crystalline picrates.

Sodium borohydride reduction of the benzylidene compound XVIII

Compound XVIII 0.2g was dissolved in 10 ml of ethanol. A solution of 0.25g of sodium borohydride in 10 ml of ethanol was added dropwise to the stirred solution of compound XVIII. Stirring was continued for two hours after the addition of the borohydride solution. The reaction mixture was allowed to stand overnight. Acetone and then water were added to the solution. Concentration to a small volume gave an aqueous suspension which was extracted with chloroform. The chloroform solution was taken to dryness and the residue dissolved in ether. Crystallization from ether yielded 0.15g of compound XLII (m.p. 190-192°). The infrared spectrum of XLII showed hydroxyl (3430 $cm^{-1}$) and cyanamide (2210 $cm^{-1}$) absorption.

Ozonolysis of compound XLII

Compound XLII (0.24g) was dissolved in methanol. A stream of oxygen containing approximately 5% ozone was passed through the solution at a rate of 50 ml/min. for 40 min. The solution was maintained at a

temperature of -30°. It was then shaken for five hours, in the presence of platinum oxide, in an atmosphere of hydrogen at a pressure of 35 lb/sq. in. Evaporation of the filtered solution yielded a residue which was dissolved in ether. Crystallization furnished 0.12g of a compound identical to XXXVII as shown by a mixed melting point determination and comparison of their infrared spectra.

Sodium borohydride reduction of compound XXXVII

Compound XXXVII (0.16g) was dissolved in approximately 15 ml of ethanol. A solution of 0.25g of sodium borohydride in ethanol was added dropwise to the stirred solution of compound XXXVII. The reaction mixture was stirred for six hours after the addition of the borohydride solution and was then allowed to stand overnight. The excess hydride was destroyed by adding acetone. The reaction mixture after the addition of water was concentrated to a small volume and extracted with chloroform. The chloroform solution was taken to dryness under reduced pressure and the residue was dissolved in ether. Crystallization gave 0.12g of material which was identical with compound XLII obtained on sodium borohydride reduction of the benzylidene compound XVIII. The melting point of the two compounds was not depressed on admixture and their infrared spectra were identical. The ultraviolet spectrum of compound XLII had $\lambda max = 260 m\mu$, $\epsilon = 380$.

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